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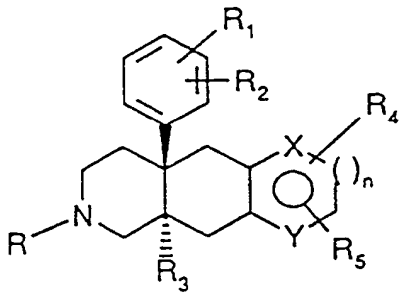
(54) **Title:** HYDROISOQUINOLINE DERIVATIVES

(57) **Abstract**

Tricyclic derivatives of octahydroisoquinoline of formula (I), wherein n is zero or 1 and if n is zero, one of X or Y is NH, oxygen or sulphur, and the other is NH, CH or a R_4- or R_5-substituted carbon atom; if n is 1, then X and Y are both nitrogen, or one of them is nitrogen and the other is CH or an R_4- or R_5-substituted carbon atom, have selective receptor agonist or antagonist activity, and are of potential therapeutic utility as analgesics or immunomodulating and/or cardiovascular agents.



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HYDROISOQUINOLINE DERIVATIVES

This invention is concerned with novel hydroisoquinoline derivatives, processes for their preparation, and their use in medicine.

The presence of at least three populations of opioid receptors (μ, δ and kappa) is now well established and documented and all three appear to be present in the central and peripheral nervous system of many species, including man (Lord J.A.H. et al., Nature 1977, 267, 495).

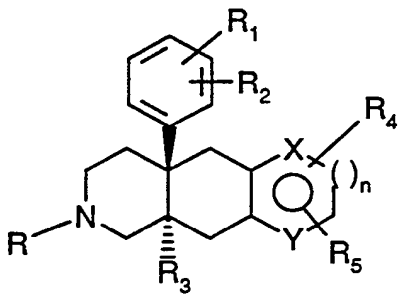
Activation of all 3 opioid receptor subtypes can lead to antinociception in animal models. In particular, studies with peptidic δ agonists have indicated that activation of the δ receptor produces antinociceptive activity in rodents and primates, and can induce clinical analgesia in man (Yaksh T.L. and Onofrio, B.M., Lancet 1983, 1386). Some experiments suggest that these δ analgesics may also lack the usual side-effects associated with μ and kappa receptor activation (Galligan et at, J. Pharm. Exp. Ther. 1984, 229, 641).

Octahydroisoquinoline derivatives having selectivity for the δ receptor have already been described. All the known derivatives are characterized by bicyclic heterocycle systems condensed at the isoquinoline ring. For example, octahydroisoquinoline derivatives are disclosed in EP-A-0,485,636 (Toray Ind.); JP-A-4,368,384, (Toray Ind.), whereas quinoline- and quinoxaline-octahydroisoquinoline derivatives are disclosed in JP-A- 6,275,288 (Toray Ind.). In WO 93/01186 (Dr. Lo Zambeletti), indole-, benzofuro- or quinolino-octahydroisoquinoline derivatives are disclosed.

A structural characteristic of the compounds disclosed in the documents mentioned above, therefore, is the presence of a condensed tetracyclic system.

A novel class of tricyclic derivatives of octahydroisoquinoline condensed with monocyclic heterocycles has now been found, characterised by a selective δ receptor agonistic or antagonistic activity. These derivatives are therefore of potential therapeutic utility as analgesics or immunomodulating and/or cardiovascular agents.

According to the present invention, there is provided a compound, or solvate or salt thereof, of formula (I):



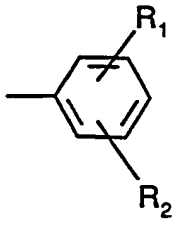
(I)

wherein:

R is hydrogen or a straight or branched C_1-C_5 alkyl, C_3-C_7 cycloalkyl, C_4-C_6 cycloalkylalkyl, C_3-C_5 alkenyl, aryl, aralkyl or furan-2-yl-alkyl;

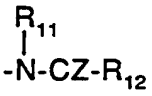
R_1 and R_2, which can be the same or different, are each hydrogen, hydroxy, C_1-C_3 alkoxy, preferably methoxy, halogen, SH, C_1-C_4-alkylthio, NHR_6, NR_6R_7, $NHCOR_6$, $NHSO_2R_6$, wherein R_6 and R_7, which are the same or different, are hydrogen or C_1-C_6 alkyl;

R_3 is hydrogen, hydroxy or C_1-C_3 alkoxy, preferably methoxy;

R_4 is a  group

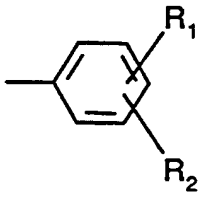
(R_1 and R_2 having the meanings defined above) or a -C(Z)-R_8 group, in which Z is oxygen or sulphur, and R_8 is C_1-C_{18}-alkyl, C_1-C_{18}-alkoxy or NR_9R_{10}, wherein R_9 and R_{10}, which may be the same or different, are hydrogen, straight or branched C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_4-C_6 cycloalkylalkyl, C_3-C_6 alkenyl, aryl, aralkyl or an optionally substituted heterocyclic ring or, taken together with the nitrogen atom which they are linked to, they form an alkylene chain having from 2 to 5 carbon atoms, optionally interrupted by an oxygen or nitrogen atom;

or R_4 is a group



in which R_{11} and R_{12} are the same as R_9 and R_{10} respectively, and Z is as defined above;

R_5 is hydrogen, C_1-C_{18} alkyl, C_2-C_{18} alkenyl, trifluoromethyl or is a

 group

(R_1 and R_2 having the meanings defined above);

n is zero or 1;

if n is zero, one of X or Y is NH, oxygen or sulphur, and the other is NH, CH or a R_4- or R_5-substituted carbon atom; if n is 1, then X and Y are both nitrogen, or one of them is nitrogen and the other is CH or a R_4- or R_5-substituted carbon atom.

When R is aryl, it is preferably phenyl, and when it is aralkyl, it is preferably phenyl-C_1-C_6 alkyl.

Examples of R are hydrogen, methyl, ethyl, cyclopropylmethyl, propyl, 2-furylmethyl and 2-phenylethyl.

Examples of R_1 and R_2 are hydrogen, hydroxy, methoxy, chlorine, bromine, fluorine, SH, methylthio, amino, methylamino, ethylamino, dimethylamino, diethylamino, diisopropylamino, methylisopropylamino, acetylamino and sulfonylamino, at any position of the ring.

Examples of R_6 and R_7 groups are hydrogen, methyl, ethyl, n-propyl, isopropyl and n-butyl.

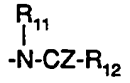
Examples of R_8 groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-heptyl, n-undecyl, n-tridecyl, n-heptadecyl, methoxy, ethoxy, propoxy, isopropoxy, hexyloxy, decyloxy, amino, methylamino, dimethylamino, diethylamino.

Examples of R_4 are ethoxycarbonyl, i-butyloxycarbonyl, aminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, di-n-propylaminocarbonyl, di-i-propylaminocarbonyl, pyrrolidinocarbonyl, benzylaminocarbonyl, phenylaminocarbonyl, morpholinocarbonyl, N-ethyl-N-i-isopropylaminocarbonyl, diethylaminothiocarbonyl, phenyl.

Examples of R_5 groups are hydrogen, methyl, ethyl, propyl, butyl, hexyl, octyl, decyl, dodecyl, octadecyl, allyl, trifluoromethyl and phenyl.

Examples of R_9 and R_{10} are hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, allyl, benzyl, phenyl, pyrrole, furan and pyridine.

Examples of the group



are acetamido, propionamido, isobutyramido and benzamido.

A first group of preferred compounds of formula (I) is one in which n is zero, X is NH and Y is CH or a R_4- or R_5-substituted carbon atom.

A second group of preferred compounds of formula (I) is one in which n is zero, X is CH or a R_4- or R_5-substituted carbon atom and Y is NH.

A third group of preferred compounds of formula (I) is one in which n is zero, X is a sulphur or oxygen atom and Y is CH or a R_4- or R_5-substituted carbon atom.

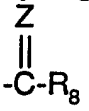
A fourth group of preferred compounds of formula (I) is one in which n is zero, X is CH or a R_4- or R_5-substituted carbon atom, and Y is an oxygen or sulphur atom.

A fifth group of preferred compounds of formula (I) is one in which n is 1, X is a nitrogen atom and Y is CH or a R_4- or R_5-substituted carbon atom.

A sixth group of preferred compounds of formula (I) is one in which n is 1, X

is CH or a R_4- or R_5-substituted carbon atom and Y is a nitrogen atom.

Particularly preferred compounds of formula (I) are those in which R_5 is hydrogen and R_4 is a



group

wherein R_8 is a C_1-C_6 alkyl, C_1-C_4 alkoxy or -NR_6R_7 group, R_6 or R_7 being as defined above.

Most preferred compounds are those in which R_8 is a -NR_6R_7 group and Z is oxygen.

The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula (I) or its salt or solvate.

One preferred pharmaceutically acceptable form is the crystalline form, including such form in a pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Examples of pharmaceutically acceptable salts of a compound of formula (I) include acid addition salts with the conventional pharmaceutical acids, for example, maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic acids.

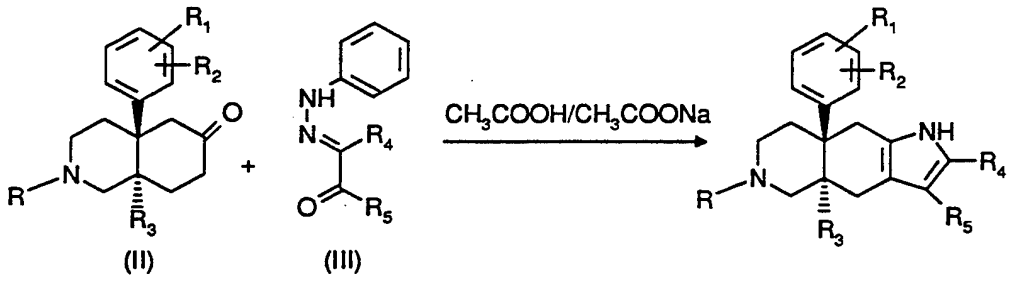
Examples of pharmaceutically acceptable solvates of a compound of formula (I) include hydrates.

The compounds of formula (I) may exist as cis or trans isomers, and the invention extends to both such forms as well as to their single enantiomers and to mixtures thereof, including racemates.

The invention also provides processes for the preparation of the compounds of formula (I).

Compounds of formula (I) in which n is zero, X is NH and Y is a R_5-substituted carbon atom, are obtained by cyclization of ketones of formula (II) (J. Org. Chem. 54, 1442 (1989)) with hydrazones of formula (III), working in the presence of metal zinc in acetic buffer, analogously to the method described in Khimiya Geterot. Soed. 342-4, 1972; see **scheme 1**:

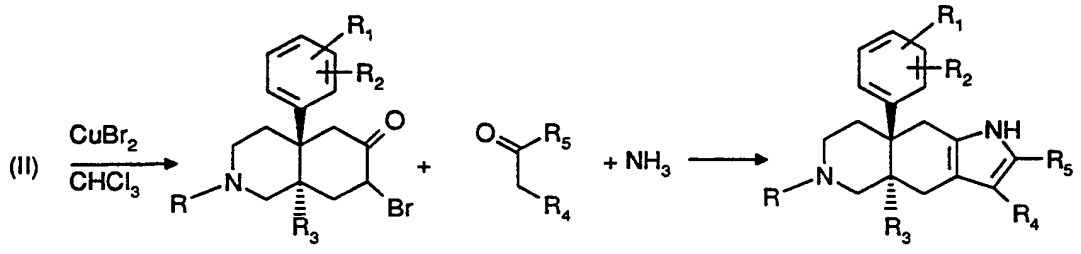
Scheme 1



(II) (III)

Compounds of formula (I) in which n is zero, X is NH and Y is a R_4-substituted carbon atom, are obtained by cyclization of bromoketones of formula (IV) (which may be obtained from ketones (II) by reaction with cupric bromide in chloroform, analogously to the method described in J. Org. Chem. 29, 3459 (1964)), with ketones (V) in the presence of ammonia, analogously to the method described in Can. J. Chem. 48, 1689 (1970); see **scheme 2**:

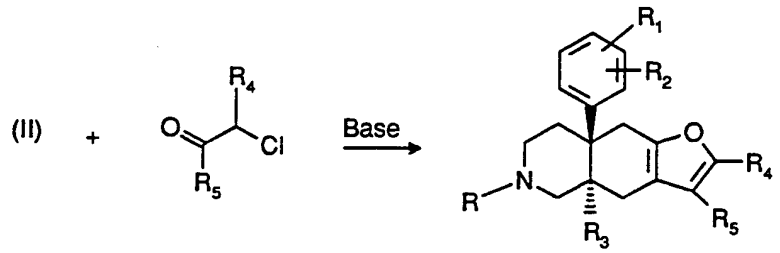
Scheme 2



(IV) (V)

Compounds of formula (I) in which n is zero, X is oxygen and Y is a R_5-substituted carbon atom, are obtained by cyclization of ketones (II) with α-haloketones (preferably α-chloroketones) (VI), in the presence of bases, analogously to the method described in J. Org. Chem. 49, 2317 (1984); see **scheme 3**:

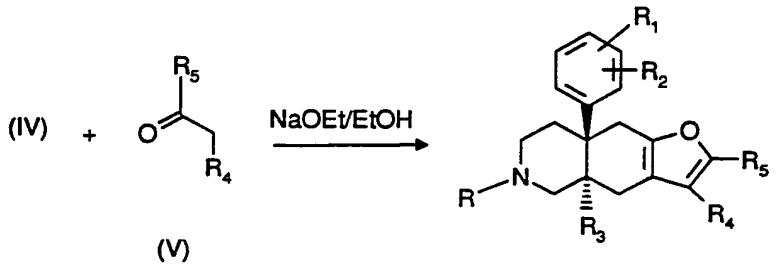
Scheme 3



(VI)

Compounds of formula (I) in which n is zero, X is oxygen and Y is a R_4-substituted carbon atom, are obtained by cyclization of bromoketones (IV) with ketones (V) in ethanol, in the presence of a base (suitably sodium ethoxide) analogously to the method described in J. Chem. Soc. Perkin I, 2372, (1972); see **scheme 4**:

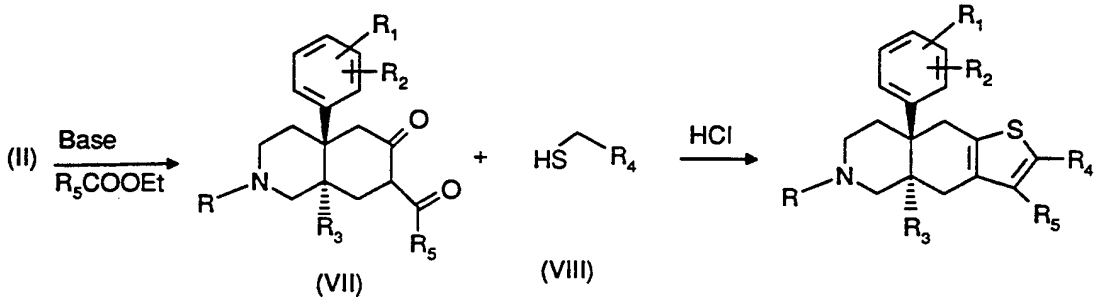
Scheme 4



(V)

Compounds of formula (I) in which n is zero, X is sulphur and Y is a R_5 substituted carbon atom, are obtained by reacting ß-diketones (VII) (which can be prepared by Claisen condensation from ketones (II) and esters of formula R_5-COOEt; J. Am. Chem. Soc. 67, 1510, 1945) with mercaptans (VIII) in the presence of hydrochloric acid, analogously to the method described in DE 1.088.507 (C.A. 56, 456 (1962)); see **scheme 5**:

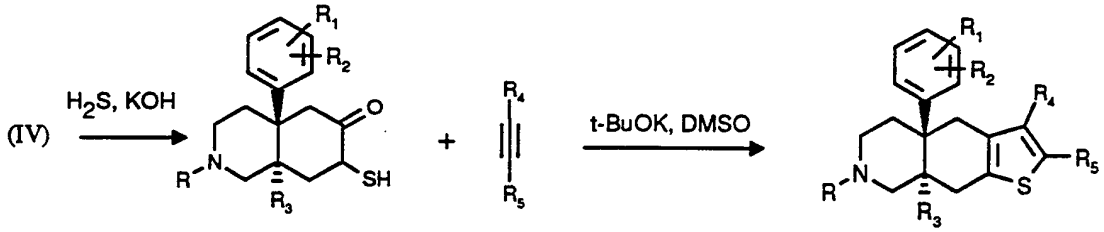
Scheme 5



(VII) (VIII)

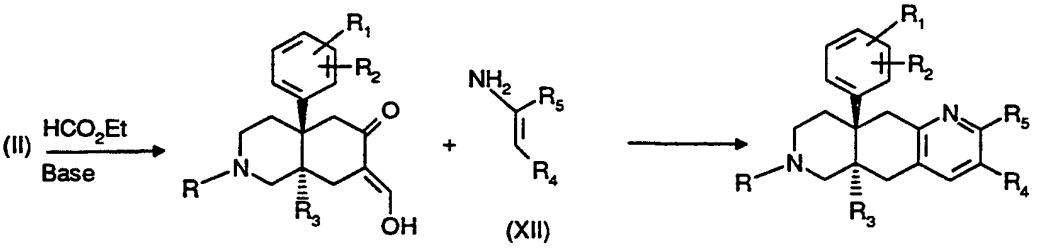
Compounds of formula (I) in which n is zero, Y is sulphur and X is a R_4-substituted carbon atom are obtained by reacting α-mercaptoketones (IX) (which are prepared starting from bromoketones (IV) and H_2S in potassium hydroxide (J. Am. Chem. Soc. 107, 4175 (1985)) with acetylene derivatives (X), in aprotic solvents (preferably dimethylsulfoxide) in the presence of bases such as potassium tert-butoxide, as described in Chem. Ber. 97, 2109 (1964); see **scheme 6**:

Scheme 6



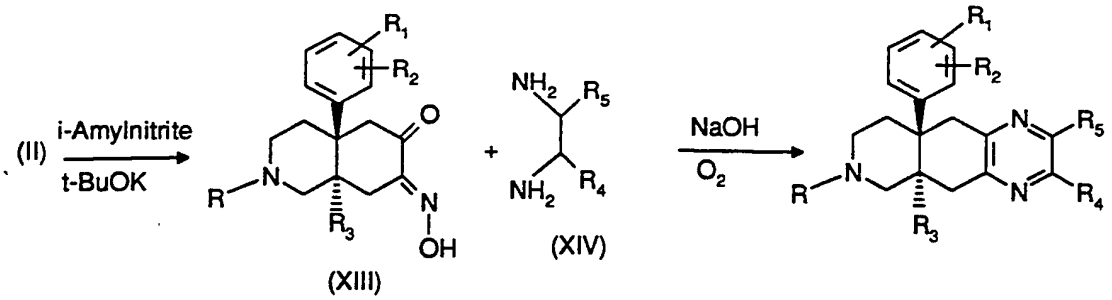
Compounds of formula (I) in which n is 1, X is a nitrogen atom and Y is CH are obtained by reacting hydroxymethyleneketones (XI) (which can be prepared from ketones (II) by condensation with ethyl formate in the presence of a base; Org. Synth. Coll. Vol. 4, 536, 1963) with enamine (XII), analogously to the method described in J. Ind. Chem. Soc. 12, 289 (1935); see **scheme 7**:

Scheme 7



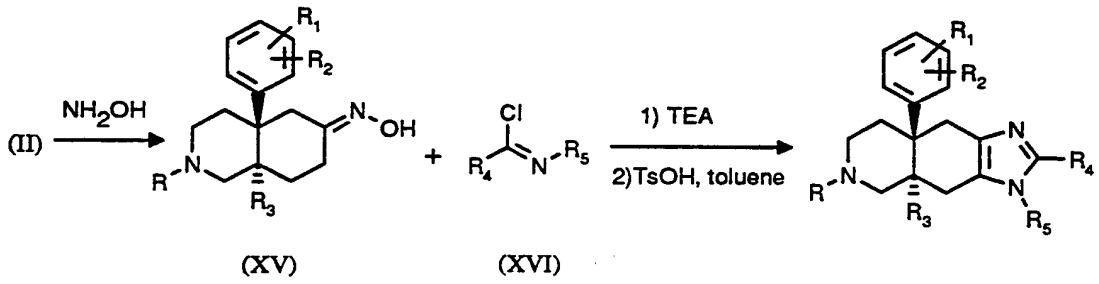
Compounds of formula (I) in which n is 1 and both X and Y are nitrogen atoms are obtained according to the invention by reacting of α-hydroxyiminoketones (XIII) (which can be prepared by reacting ketones (II) with isoamyl nitrite and potassium tert-butoxide; J. Med. Chem. 34, 1715, 1991) with ethanediamine (XIV) and subsequent aromatization of the intermediate by oxidation in basic medium, analogously to the method described in Chem. Ber. 100, 555 (1967); see **scheme 8**:

Scheme 8

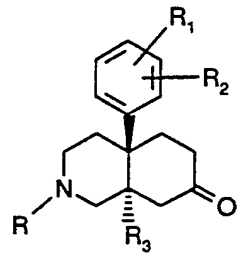


Compounds of formula (I) in which n = 0, X and Y are both N, may be obtained from hydroxyimino derivatives (XV) and R_4- R_5-substituted chloroimidates of formula (XVI) in basic media, and subsequent treatment of the intermediates with H^+ in refluxing toluene (J. Org. Chem., 58, 7092, (1993)) as described in scheme 9:

Scheme 9



The compounds of formula (I) in which n is zero, Y is an heteroatom and X is a R_4- or R_5-substituted carbon atom (or in which n is 1, X and Y are both nitrogen atoms and the substituents R_5 and R_4 are reversed) can be obtained according to analogous schemes to those shown above, starting from isomer ketones of formula (IIa)



(IIa)

which can in their turn be obtained according to the method described in J. Med.

Chem. 35, 48 (1992).

The processes of the invention also comprise the conversions of substituent groups into other substituent groups, carried out according to per se known methods, on the final compounds (I): for example demethylation of methoxy groups to hydroxy groups, or alkylation of the latter or of SH or NH groups, and the like.

As mentioned before, the compounds of formula (I) exist in more than one stereoisomeric form and the process of the invention produces mixtures thereof.

The individual isomers may be obtained from the enantiomerically pure intermediates.

The individual forms of the compounds of formula (I) may be separated one from another by resolution using an optically active acid such as tartaric acid or O,O'-di-p-toluoyltartaric acid. Alternatively, the single enantiomers can be prepared by an asymmetric synthesis.

The compounds of formula (I) may be converted into their pharmaceutically acceptable acid addition salts by reaction with the appropriate organic or mineral acids.

Solvates of the compounds of formula (I) may be formed by crystallisation or recrystallisation from the appropriate solvent. For example hydrates may be formed by crystallisation or recrystallisation from aqueous solutions or solutions in organic solvents containing water.

The salts or the solvates of the compounds of formula (I) which are not pharmaceutically acceptable can also be useful as intermediates in the preparation of pharmaceutically acceptable salts or solvates. Therefore, said salts or solvates are also part of this invention.

The activity of compounds of formula (I) in standard tests shows they are of potential therapeutic utility in the treatment of pain, in the prevention of rejection in organ transplants and skin grafts and, generally, for the treatment of pathological conditions which can be treated or alleviated by opioid δ receptor agonists or antagonists.

Accordingly the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

The present invention further provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of pain, for the prevention of the rejection of organ transplants and skin grafts and, generally, for the treatment of pathological conditions

which can be treated or alleviated by opioid δ receptor agonists or antagonists. Such a medicament, and a composition of this invention, may be prepared by admixture of a compound of the invention with an appropriate carrier. It may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the preparation of compositions of known analgesic agents.

Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form suitable for use in the medical or veterinarian fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of pain, as an immunomodulating and/or immunosuppressive agent and, generally, as opioid δ receptor agonists or antagonists agents.

The suitable dosage range for the compounds of the invention depends on the compound to be employed and on the condition of the patient. It will also depend, *inter alia*, upon the relation of potency to adsorbability and the frequency and route of administration.

The compound or composition of the invention may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinyl-pyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk.

Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if desired with a carrier or other excipients.

Liquid compositions for oral administration may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The compounds of this invention may also be administered by non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as a suppository. They may also be formulated, for presentation in an injectable form, in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to make the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle from which the appropriate dose may be withdrawn, or a solid form or concentrate which can be used to prepare an injectable formulation.

As mentioned earlier, the effective dose of compound depends on the particular compound employed, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day, for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20 mg of active ingredient and be administered in multiple doses, if desired, to give the above mentioned daily dose.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

The present invention also provides a method for the treatment and/or prophylaxis of pain and of rejection of transplants and skin grafts in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

Compounds of this invention and their preparation are illustrated in the following Examples, the preparation of intermediates being illustrated in the Preparations.

PREPARATION 1

N,N-Diethyl-3-oxobutyramide

40 g (0.31 mol) of ethyl acetoacetate and 24 g (0.33 mol) of diethylamine were stirred in a Parr apparatus at 150 °C for 10'. The crude mixture was distilled at 115-120°C / 9 mmHg, to give 32 g of the title compound.

$C_8H_{15}NO_2$

IR (neat): 2980, 1725, 1640, 1590 cm^{-1}.

N.M.R. 80 MHz ($CDCl_3$): δ 3.6-3.1 (m, 6H); 2.2 (s, 3H), 1.1 (dt, 6H).

PREPARATION 2

N,N-Diethyl-2-phenylhydrazono-3-oxobutyramide

15.7 g (0.1 mol) of N,N-diethyl-3-oxobutyramide were mixed with 12 g (0.14 mol) of CH_3COONa, 20 ml of water and 75 ml of ethanol. The solution obtained was cooled to 10 °C and 0.1 mol of freshly prepared solution of phenyldiazonium chloride [Organic Reactions, R. Adams Ed; Wiley, New York, **10**, 32-33, (1951-1959)] were added dropwise. The precipitated solid was filtered, dried *in vacuo* yielding 22.6 g of the title compound. M.p. = 63-65 °C.

$C_{14}H_{19}N_3O_2$

IR (neat): 2970, 1720, 1620, 1605, 1560, 1245 cm^{-1}.

N.M.R. 300 MHz ($CDCl_3$): δ 9.3 (s, 1H); 7.4-7.2 (m, 5H); 3.6 (q, 2H); 3.2 (q, 2H); 2.5 (s, 3H); 1.35 (t, 3H); 1.2 (t, 3H).

MS (TSP) m/z = 262.1 (MH^+)

PREPARATION 3

N,N-Dipropyl-3-oxobutyramide

43.4 g (43.3 mol) of ethyl acetoacetate and 33.7 g (43.3 mol) of dipropylamine were treated as described in preparation 1. The crude oil was distilled at 86-89 °C / 0.8 mmHg, to give 44.3 g of the title compound.

$C_{10}H_{19}NO_2$

I.R. (neat): 2980, 1725, 1640, 1590 cm^{-1}.

N.M.R. 80 MHz ($CDCl_3$): δ 3.45 (s, 2H), 3.4-2.9 (m, 4H), 2.3 (s, 3H), 1.7-1.2 (m, 4H), 0.9-0.6 (t, 6H).

MS (TSP) m/z = 186.3 (MH^+)

PREPARATION 4

N,N-Dipropyl-2-phenylhydrazono-3-oxobutyramide

18.5 g (0.1 mol) of N,N-dipropyl-3-oxobutyramide, 12 g (0.146 mol) of CH_3COONa, 20 ml of water, 75 ml of ethanol and a solution of 0.1 mol of phenyldiazonium chloride were treated as described in preparation 2. The precipitated solid was filtered and dried *in vacuo* yielding 4.2 g of the title compound. M.p. = 79-80 °C.

$C_{16}H_{23}N_3O_2$

I.R. (KBr): 2970, 1670, 1610, 1495 cm^{-1}

N.M.R. 300 MHz ($CDCl_3$): δ 7.3 (s, 1H), 7.4-7.0 (m, 5H), 3.5-3.1 (st, 4H), 2.5 (s, 3H), 1.75-1.5 (m, 4H), 1.0 (t, 3H), 0.75 (t, 3H).

MS (TSP) m/z = 290.4 (MH^+)

PREPARATION 5

i-Butyl acetoacetate

30 ml of ethyl acetoacetate were dissolved in 350 ml of *i*-butyl alcohol and a catalytic amount of *p*-toluensulphonic acid (PTSA) was added. The solution was refluxed for 18 h. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in ether. The resulted solution was treated with s.s. $NaHCO_3$. The organic layer was separated, dried over Na_2SO_4 and evaporated *in vacuo*. The crude oil was distilled at 66-68 °C / 4 mmHg, to give 18.8 g of the title compound.

$C_8H_{14}O_3$

MS (TSP) m/z = 159.3 (MH^+)

PREPARATION 6

i-Butyl 2-phenylhydrazono-3-oxobutyrate

15.8 g (0.1 mol) of *i*-butyl acetoacetate, 12 g (0.146 mol) of CH_3COONa, 20 ml of water, 75 ml of ethanol and a solution of 0.1 mol of phenyldiazonium chloride were treated as described in preparation 2. The precipitated solid was filtered an dried *in vacuo* yielding 23.1 g of the title compound. M.p. = 45-50 °C.

$C_{14}H_{18}N_2O_3$

I.R. (KBr): 2970, 1690, 1600, 1530 cm^{-1}N.M.R. 300 MHz ($CDCl_3$): δ 10-9.2 (bs, 1H), 7.4-7.1 (m, 5H), 4.1 (d, 4H), 2.5 (s, 3H), 1.75-1.5 (m, 4H), 1.0 (t, 3H), 0.75 (t, 3H).

MS (TSP) m/z = 263.3 (MH^+)

PREPARATION 7

N-Benzyl-3-oxobutyramide

9 ml (0.05 mol) of 2,2,6-trimethyl-4H-1,3-dioxin-4-one (diketene-acetone adduct) were added dropwise to a solution of 5.5 ml (0.05 mol) of benzylamine in 20 ml of toluene and the temperature was allowed to rise 70 °C. The solution was refluxed for 2 h then the solvent was removed *in vacuo*. The crude product was triturated with ether obtaining 7.5 g of the title compound. M.p. = 84-86 °C.

$C_{11}H_{13}NO_2$

I.R. (KBr): 3250, 3080, 1720, 1645 cm^{-1}

PREPARATION 8

N-Benzyl-2-phenylhydrazono-3-oxobutyramide

7.27 g (0.038) of N-benzyl-3-oxobutyramide were dissolved in a solution of 5.32 g (0.133 mol) of NaOH in 58 ml of water. To the ice-cooled stirred solution, 0.040 mol of phenyldiazonium chloride were added dropwise at such a rate as to keep the temperature at 0 °C. The precipitated solid was filtered and recrystallised from MeOH yielding 9 g of the title compound. M.p. = 101-103 °C.

$C_{17}H_{17}N_3O_2$

I.R. (KBr): 3300, 1650, 1510, 1245 cm^{-1}

PREPARATION 9

1-(3-Oxobutyryl)pyrrolidine

9 ml (0.05 mol) of diketene-acetone adduct and a solution of 4.2 ml (0.05 mol) of pyrrolidine in 20 ml of toluene were treated as described in preparation 7. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel (EtOAc/MeOH 0%→1%) yielding 7.6 g of the title compound as a dark oil.

$C_8H_{13}NO_2$

I.R. (neat): 2980, 2880, 1725, 1645 cm^{-1}

MS (TSP) m/z = 156 (MH^+)

PREPARATION 10

1-(2-Phenylhydrazono-3-oxobutyryl)pyrrolidine

7.6 g (0.049 mol) of 1-(3-oxobutyryl)pyrrolidine, a solution of 6.86 g (0.17 mol) of NaOH in 75 ml of water and 0.051 mol of phenyldiazonium chloride were treated as described in preparation 8. The crude reaction mixture was purified by

chromatography on silica gel (Et_2O) obtaining 8 g of the title compound which was used as such in the subsequent step.

PREPARATION 11

N-Phenyl-2-phenylhydrazono-3-oxobutyramide

4.5 g (25.4 mmol) of acetoacetanilide, a solution of 3.46 g (89 mmol) of NaOH in 45 ml of water and 95 mmol of phenyldiazonium chloride were treated as described in preparation 8. The residue was crystallised from EtOH, yielding 3.4 g of the title compound. M.p. = 96-97 °C.

$C_{16}H_{15}N_3O_2$

I.R. (KBr): 3080, 1675, 1600, 1520 cm^{-1}

MS (TSP) m/z = 282.2 (MH^+)

PREPARATION 12

N,N-Dimethyl-3-oxobutyramide

A solution of 9 ml (0.05 mmol) of diketene-acetone adduct in 20 ml of toluene was treated with gaseous dimethylamine at room temperature until the reaction was complete. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel (EtOAc/MeOH 0%→10%) yielding 7.0 g of the title compound.

$C_6H_{11}NO_2$

I.R. (neat): 2940, 1720, 1640 cm^{-1}

PREPARATION 13

N,N-Dimethyl-2-phenylhydrazono-3-oxobutyramide

4.5 g (0.035 mol) of N,N-dimethyl-3-oxobutyramide, a solution of 4.9 g (0.122 mol) of NaOH in 45 ml of water and 0.037 mol of phenyldiazonium chloride were treated as described in preparation 8. The crude reaction mixture was purified by chromatography on silica gel (hexane/Et_2O 0%→100%) obtaining 3.5 g of the title compound which was used as such in the subsequent step. M.p. = 131-133 °C.

$C_{12}H_{15}N_3O_2$

I.R. (KBr): 3205, 1720, 1630, 1565 cm^{-1}

PREPARATION 14

3-Oxobutyramide

A solution of 9 ml (0.05 mmol) of diketene-acetone adduct in 20 ml of toluene was treated with gaseous ammonia as described in preparation 12. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel (EtOAc) yielding 5.0 g of the title compound.

$C_4H_7NO_2$

I.R. (neat): 3300, 1730, 1640 cm^{-1}

PREPARATION 15

2-Phenylhydrazono-3-oxobutyramide

5.0 g (0.049 mol) of 3-oxobutyramide, a solution of 6.9 g (0.171 mol) of NaOH in 75 ml of water and 0.051 mol of phenyldiazonium chloride were treated as described in preparation 8. The crude reaction mixture was purified by chromatography on silica gel (EtOAc) obtaining 3 g of the title compound which was used as such in the subsequent step. M.p. = 146-147 °C.

$C_{10}H_{11}N_3O_2$

I.R. (KBr): 3320, 1720, 1520 cm^{-1}

PREPARATION 16

N,N-Diisopropyl-3-oxobutyramide

9 ml (0.05 mol) of diketene-acetone adduct and a solution of 47.0 ml (0.05 mol) of diisopropylamine in 20 ml of toluene were treated as described in preparation 7. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel (Et_2O) yielding 7.0 g of the title compound as a dark oil.

$C_{10}H_{19}NO_2$

I.R. (neat): 2980, 1725, 1640 cm^{-1}

PREPARATION 17

N,N-Diisopropyl-2-phenylhydrazono-3-oxobutyramide

7.0 g (0.038 mol) of N,N-diisopropyl-3-oxobutyramide, a solution of 5.3 g (0.133 mol) of NaOH in 58 ml of water and 0.04 mol of phenyldiazonium chloride were treated as described in preparation 8. The crude reaction mixture was purified by chromatography on silica gel (hexane/Et_2O 95:5) obtaining 7.5 g of the title compound which was used as such in the subsequent step. M.p. = 143-145 °C.

$C_{16}H_{23}N_3O_2$
I.R. (KBr): 3210, 2980, 1650, 1620 cm^{-1}

PREPARATION 18

Ethyl 2-phenylhydrazono-4,4,4-trifluoro-3-oxobutyrate

7.3 ml (0.05 mol) of ethyl 3-oxo-4,4,4-trifluoroacetoacetate, 6 g (0.073 mol) of CH_3COONa, 20 ml of water, 37.5 ml of ethanol and a solution of 0.05 mol of phenyldiazonium chloride were treated as described in preparation 2. The crude product was purified by chromatography on silica gel (hexane/Et_2O 0%→25%) obtaining 8.65 g of the title compound. M.p. = 78-80 °C.
$C_{12}H_{11}F_3N_2O_3$
I.R. (KBr): 1710, 1530 cm^{-1}
N.M.R. 300 MHz (DMSO-d_6): δ 12.8 (s, 1H), 7.8-7.2 (m, 5H), 4.2 (q, 2H), 1.5 (t, 3H). MS (EI) m/z = 288.0 (M^+).

PREPARATION 19

(±)-trans-4a-(3-Methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride

A solution of 1.2 g (4.2 mmol) of (±)-trans-2-ethyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline and 1.8 g (12.6 mmol) of proton sponge in 34 ml of 1,2-dichloroethane was treated with 1.4 ml (16.8 mmol) of vinylchloroformate at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at this temperature for 15 min and then refluxed for 3 h, the solvent was removed *in vacuo*, the residue was taken up in water and extracted with Et_2O. The organic layer was washed with 3% HCl, then was dried over Na_2SO_4 and the solvent was removed *in vacuo*. The dark residue was dissolved in EtOH, 3 ml of concentrated HCl were added and the solution refluxed for 3 hours. The solvent was removed *in vacuo*, obtaining 0.88 g of the title compound which was used as such in the subsequent step. M.p. = 90 °C dec..
$C_{16}H_{21}NO_2 \cdot HCl$
I.R. (KBr): 3400, 2970, 1715, 1600 cm^{-1}

PREPARATION 20

(±)-trans-2-Cyclopropylmethyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride

0.88 g (3.08 mmol) of (±)-trans-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-

decahydroisoquinoline hydrochloride, 0.44 g (3,23 mmol) of cyclopropylmethyl bromide, 0.64 g of potassium carbonate and a catalytical amount of potassium iodide in 15.4 ml of DMF were stirred at 60 °C for 2 h. The solvent was removed *in vacuo*, and the crude product was purified by flash chromatography (EtOAc/MeOH/conc.NH_4OH 90:10:0.8). The solid product was dissolved in acetone and the solution brought to acidic pH with HCl/Et_2O. The precipitate was filtered, yielding 0.28 g of the title compound. M.p. = 78 °C dec.

$C_{20}H_{27}NO_2 \cdot HCl$

I.R. (KBr): 3400, 2940, 1715, 1600 cm^{-1}

N.M.R. 300 MHz (DMSO-d_6): δ 7.4-6.8 (m, 4H), 3.8 (s, 3H), 3.6-1.1 (m, 16H), 0.6 (m, 2H), 0.4 (m, 2H).

MS (EI) m/z = 314.2 (MH^+).

PREPARATION 21

(±)-trans-2-Diethylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

A solution of 0.6 g (1.42 mmol) of (±)-trans-2-diethylaminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride and 0.6 g (2.48 mmol) of proton sponge in 35 ml of 1,2-dichloroethane was treated with 0.245 ml (2.48 mmol) of vinylchloroformate and then with conc. HCl in EtOH as described in preparation 19, obtaining 0.36 g of the title compound.

$C_{24}H_{33}N_3O_2 \cdot HCl$

I.R. (KBr): 3400, 2970, 1755, 1600 cm^{-1}

PREPARATION 22

(±)-trans-2-Butyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline

0.71 g (2.55 mmol) of (±)-trans-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride, 0.37 g (2.68 mmol) of butyl bromide, 0.53 g of potassium carbonate and a catalytical amount of potassium iodide in 15 ml of DMF were reacted as described in preparation 20, yielding 0.2 g of the title compound which was used as such in the subsequent step.

$C_{20}H_{29}NO_2$

I.R. (neat): 3400, 2930, 1715, 1605 cm^{-1}

PREPARATION 23

(±)-trans-2-Ethyl-6-hydroxyimino-4a-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline

0.5 g (1.54 mmol) of (±)-trans-2-ethyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride, 0.456 g (6.56 mmol) of hydroxylamine hydrochloride and 0.64 g of $KHCO_3$ in 10 ml of MeOH were refluxed for 45 min. The precipitate was filtered, the solvent was removed *in vacuo* and the residue taken up in H_2O. The pH was adjusted to 8 with conc. NH_4OH, the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried, the solvent removed *in vacuo*, obtaining 0.45 g of the title compound which was used as such in the subsequent step.

$C_{18}H_{26}N_2O_2$

I.R. (KBr): 2940, 2820, 1605, 1580 cm^{-1}

PREPARATION 24

(±)-trans-2-Diisopropylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

A solution of 0.57 g (1.26 mmol) of (±)-trans-2-diisopropylaminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline and 0.54 g (4.52 mmol) of proton sponge in 35 ml of 1,2-dichloroethane was treated with 0.77 ml (4.52 mmol) of vinyl chloroformate and then with conc. HCl in EtOH as described in preparation 19, obtaining 0.34 g of the title compound.

$C_{26}H_{37}N_3O_2 \cdot HCl$

I.R. (KBr): 3400, 2970, 1755, 1600 cm^{-1}

EXAMPLE 1

(±)-trans-2-Diethylaminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline

1.6 g (4.9 mmol) of (±)-trans-2-ethyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride (*J. Med. Chem.*, **54**, 1442, 1989) and 1.54 g (5.8 mmol) of N,N-diethyl-2-phenylhydrazono-3-oxobutyramide were dissolved in a mixture of 5 ml of glacial acetic acid and 0.48 g (5.8 mmol) of CH_3COONa. The solution was heated to 60 °C then, under N_2 atmosphere, 1.47 g (22.5 mmol) of zinc dust were added portionwise. The resulting mixture was refluxed for 2 h and cooled to room temperature. The precipitate was removed by decantation and washed with 5 ml of glacial acetic acid. The combined acidic solutions were diluted with iced water (50 ml), the pH was adjusted to 8 with 20% NaOH and then extracted with AcOEt. The organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (AcOEt/MeOH/conc. NH_4OH 90:10:1; Rf = 0.25), yielding 1.4 g of the title compound. M.p. (HCl salt) = 247 °C dec.

$C_{26}H_{37}N_3O_2$

I.R. (KBr) (·HCl): 3410, 3200, 2920, 2500, 1600, 1580 cm^{-1}.

N.M.R. 80 MHz ($CDCl_3$): δ 7.3 (s, 1H), 7.2-6.6 (m, 4H), 3.7 (s, 3H), 3.6-2.0 (m, 20H), 1.95 (s,3H), 1.2-0.9 (m, 6H).

MS (TSP) m/z = 424.2 (MH^+)

EXAMPLE 2

(±)-trans-2-Diethylaminocarbonyl-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline

To a solution of 1.89 ml (20.2 mmol) of boron tribromide in 40 ml of dry $CHCl_3$, 1.43 g (3.37 mmol) of (±)-trans-2-diethylaminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3g] isoquinoline dissolved in 15 ml of dry $CHCl_3$ were added, under N_2 atmosphere, at room temperature. After 2 h the mixture was poured in 200 g of ice containing 20 ml of conc. NH_4OH. The organic layer was separated, dried over Na_2SO_4 and the solvent removed *in vacuo*. The residue was purified by flash chromatography (AcOEt/MeOH/conc. NH_4OH 80:20:2), obtaining 0.8 g of the title compound. M.p. = 221-223 °C

$C_{25}H_{35}N_3O_2$

I.R. (KBr): 3500, 2940, 1575, 1300 cm^{-1}.

N.M.R. 300 MHz (DMSO-d6): δ 10.25 (s, 1H), 8.55 (s, 1H), 7.0-6.8 (m, 3H), 6.45

(d, 1H), 2.85-1.85 (m, 20H), 1.95 (s, 3H), 1.0 (dt, 6H).
MS (TSP) m/z = 410.2 (MH^+)

EXAMPLE 3

(±)-trans-6-Ethyl-2-ethoxycarbonyl-3-methyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline

0.8 g (2.47 mmol) of (±)-trans-2-ethyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride and 0.87 g (93.7 mmol) of ethyl 2-phenylhydrazono-3-oxobutyrate [Organic Reactions, R. Adams Ed; Wiley, New York, **10**, 32-33, (1951-1959)] were dissolved in a mixture of 3 ml of glacial acetic acid and 0.34 g (4.2 mmol) of CH_3COONa. The solution was treated as described in example 1 adding 0.74 g (11.3 mmol) of zinc dust. The residue was purified by flash chromatography (AcOEt/MeOH/conc. NH_4OH 94:5:0.5; Rf = 0.3), obtaining 0.6 g of the title compound.
$C_{24}H_{32}N_2O_3$
I.R. (KBr): 3300, 2915, 1680, 1600, 1445 cm^{-1}
N.M.R. 300 MHz (DMSO-d6): δ 10.8 (s, 1H), 7.2-6.6 (m, 4H), 4.1 (q, 2H), 3.65 (s, 3H), 3.1-2.2 (m, 11H), 2.1 (s, 3H), 1.7 (d, 2H), 1.1(t, 3H), 0.95 (t, 3H).
MS (TSP) m/z = 397.2 (MH^+)

EXAMPLE 4

(±)-trans-6-Ethyl-2-ethoxycarbonyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline

0.6 g (1.5 mmol) of (±)-trans-6-ethyl-2-ethoxycarbonyl-3-methyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline were treated with 0.84 ml (9.0 mmol) of boron tribromide as described in example 2. The crude solid was purified by flash chromatography (AcOEt/MeOH/conc. NH_4OH 80:20:2), yielding 0.12 g of the title compound. M.p. = 195 -197 °C
$C_{23}H_{30}N_2O_3$
I.R. (KBr): 3300, 2920, 1690, 1440 cm^{-1}.
N.M.R. 300 MHz (DMSO-d6): δ 10.8 (s, 1H), 9.1 (s, 1H), 7.1-6.4 (m, 3H), 4.1 (q, 2H), 3.45-1.75 (m, 14H), 2.1 (s, 3H), 1.2 (t, 3H), 1.0 (t, 3H).
MS (TSP) m/z = 383.1 (MH^+)

EXAMPLE 5

(±)-trans-Dipropylaminocarbonyl-6-ethyl-3-methyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

0.7 g (2.16 mmol) of (±)-trans-2-ethyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride, 0.62 g (2.16 mmol) of N,N-dipropyl-2-phenylhydrazono-3-oxobutyramide, 0.21 g (2.6 mmol) of CH_3COONa, 0.65 g (10 mmol) of zinc dust and 2.5 ml of glacial acetic acid were treated as described in example 1. The residue was purified by flash chromatography (AcOEt/MeOH/conc. NH_4OH 90:10:1.5; Rf = 0.3), dissolved in Et_2O and the solution brought to acidic pH with HCl/Et_2O. The precipitate was filtered and recrystallised from a mixture of AcOEt/Acetone = 9/1, yielding 0.65 g of the title compound.

M.p. = 250 °C dec.

$C_{28}H_{41}N_3O_2 \cdot HCl$

I.R. (KBr): 3400, 3210, 2970, 1600, 1580 cm^{-1}

N.M.R. 300 MHz ($CDCl_3$): δ 12 (bs, 1H), 8.5 (s, 1H), 7.4-6.6 (m, 4H), 3.8-2.5 (m, 17H), 2.0 (s, 3H), 1.8-1.3 (m, 10H), 0.9 (t, 6H).

MS (TSP) m/z (free base)= 452.7 (MH^+)

EXAMPLE 6

(±)-trans-Dipropylaminocarbonyl-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline

0.56 g (1.15 mmol) of (±)-trans-dipropylaminocarbonyl-6-ethyl-3-methyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline hydrochloride were treated with 0.65 ml (7 mmol) of boron tribromide as described in example 2. The residue was purified by flash chromatography (AcOEt/MeOH/conc. NH_4OH 75:25:2.5). The crude product was crystallised from acetone yielding 0.075 g of the title compound. M.p. = 151-153 °C.

$C_{27}H_{39}N_3O_2$

I.R. (KBr): 3150, 2970, 1590, 1450 cm^{-1}

N.M.R. 300 MHz (DMSO-d_6): δ 10.2 (s, 1H), 9.1 (s, 1H), 7.2-6.4 (m, 4H), 3.5-1.8 (m, 17H), 1.9 (s, 3H), 1.6-1.4 (m, 4H), 1.0 (t, 3H), 0.8 (t, 6H).

MS (TSP) m/z = 438.4 (MH^+)

EXAMPLE 7

(±)-trans-2-(*i*-Butoxycarbonyl)-6-ethyl-3-methyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

0.7 g (2.16 mmol) of (±)-trans-2-ethyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride, 0.56 g (2.16 mmol) of *i*-butyl 2-phenylhydrazono-3-oxobutyrate, 0.21 g (2.6 mmol) of CH_3COONa, 0.65 g (10 mmol) of zinc dust and 2.5 ml of glacial acetic acid were treated as described in example 1. The residue was purified by flash chromatography (AcOEt/MeOH/conc. NH_4OH 90:10:1.5; Rf = 0.27). The purified free base was dissolved in AcOEt and the solution brought to acidic pH with HCl/Et_2O. The precipitate was filtered, washed and dried, to yield 0.56 g of the title compound. M.p. = 230 °C dec.

$C_{26}H_{36}N_2O_3 \cdot HCl$

I.R. (KBr): 3400, 2970, 1670, 1600 cm^{-1}

N.M.R. 300 MHz ($CDCl_3$): δ 9.7 (bs, 1H), 8.4 (s, 1H), 7.3-6.6 (m, 4H), 4.0 (d, 2H), 3.8 (s, 3H), 3.6-2.5 (m, 13H), 2.2 (s, 3H), 2.1-1.4 (m, 4H), 1.0 (d, 6H).

EXAMPLE 8

(±)-trans-2-(*i*-Butoxycarbonyl)-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

0.56 g of (±)-trans-2-(*i*-butoxycarbonyl)-6-ethyl-3-methyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride were treated with 0.68 ml (7.26 mmol) of boron tribromide as described in example 2. The residue was purified by flash chromatography (AcOEt/MeOH/conc. NH_4OH 75:25:2.5) and then crystallised from AcOEt yielding 0.1 g of the title compound.

M.p. = 196-198 °C

$C_{25}H_{34}N_2O_3$

I.R. (KBr): 2960, 1620, 1580, 1320 cm^{-1}

N.M.R. 300 MHz (DMSO-d_6): δ 9.2 (s, 1H), 8.5 (s, 1H), 7.0-6.2 (m, 4H), 3.8 (d, 2H), 3.0-1.8 (m, 14H), 2.1 (s, 3H), 1.1-0.9 (m, 9H).

MS (TSP) m/z = 411.4 (MH^+)

EXAMPLE 9

(±)-trans-2-Diethylaminocarbonyl-3,6-dimethyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline

3 g (9.3 mmol) of (±)-trans-2-ethyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride, 2.92 g (11.2 mmol) of

N,N-diethyl-2-phenylhydrazono-3-oxobutyramide, 0.92 g (11.2 mmol) of CH_3COONa, 2.8 g (42.8 mmol) of zinc dust and 9.3 ml of glacial acetic acid were treated as described in example 1. The residue was purified by flash chromatography (AcOEt/MeOH/conc. NH_4OH 90:10:1; Rf = 0.27) yielding 0.56 g of the title compound. M.p. (·HCl) = 250 °C dec.

$C_{25}H_{35}N_3O_2$

I.R. (KBr) (hydrochloride): 3410, 3200, 2915, 2510, 1605, 1580 cm^{-1}.

EXAMPLE 10

(±)-trans-2-Diethylaminocarbonyl-3,6-dimethyl-8a-(3-hydroxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

0.5 g (1.22 mmol) of (±)-trans-2-diethylaminocarbonyl-3,6-dimethyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline were treated with 0.68 ml (7.26 mmol) of boron tribromide as described in example 2. The residue was purified by flash chromatography (AcOEt/MeOH/conc. NH_4OH 75:25:2.5). The crude product was dissolved in MeOH and the solution brought to acidic pH with HCl/Et_2O. The solvent was evaporated *in vacuo* and the solid crystallised from a mixture of acetone/MeOH = 1:1, yielding 0.06 g of the title compound. M.p. = >250 °C

$C_{24}H_{33}N_3O_2 \cdot HCl$

I.R. (KBr): 3450, 3120, 2970, 1600, 1580 cm^{-1}

N.M.R. 300 MHz (DMSO-d_6): δ 10.4 (s, 1H), 9.2 (s, 1H), 7.2-6.5 (m, 4H), 3.5-2.0 (m, 15H), 2.8 (s, 3H), 1.9 (s, 3H), 1.0 (t, 6H).

MS (TSP) m/z(free base) = 396.4 (MH^+)

EXAMPLE 11

(±)-trans-2-Diethylaminocarbonyl-3,7-dimethyl-4a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[3,2-g]isoquinoline

0.9 g (2.9 mmol) of (±)-trans-2-ethyl-4a-(3-methoxyphenyl)-7-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride (*J. Med. Chem.*, **35**, 48, 1992), 0.9 g (3.5 mmol) of N,N-diethyl-2-phenylhydrazono-3-oxobutyramide, 0.28 g (3.5 mmol) of CH_3COONa, 0.87 g (13.3 mmol) of zinc dust and 5 ml of glacial acetic acid were treated as described in example 1. The residue was purified by flash chromatography (CH_2Cl_2/MeOH/conc. NH_4OH 86:10:0.6; Rf = 0.27), to yield 0.2 g of the title compound. M.p. = 153-155 °C dec.

$C_{25}H_{35}N_3O_2$

I.R. (KBr): 3250, 2920, 1605, 1580 cm^{-1}.

N.M.R. 300 MHz ($CDCl_3$): δ 8.2 (s, 1H), 7.1-6.6 (m, 4H), 3.7 (s, 3H), 3.6-1.95 (m, 15H), 2.3 (s, 3H), 1.9 (s, 3H), 1.1 (t, 6H).
MS (TSP) m/z = 410.5 (MH^+)

EXAMPLE 12
(±)-trans-2-Diethylaminocarbonyl-3,7-dimethyl-4a-(3-hydroxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[3,2-g]isoquinoline

0.29 g (0.71 mmol) of (±)-trans-2-diethylaminocarbonyl-3,7-dimethyl-4a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[3,2-g] isoquinoline were treated with 0.4 ml (4.26 mmol) of boron tribromide as described in example 2. The residue was purified by flash chromatography (CH_2Cl_2/MeOH/conc. NH_4OH 80:12:0.8). The crude product was triturated with a mixture of acetone/MeOH = 3:2, yielding 0.14 g of the title compound. M.p. = 235-238 °C
$C_{24}H_{33}N_3O_2$
I.R. (KBr): 3215, 2920, 1610, 1510 cm^{-1}
N.M.R. 300 MHz (DMSO-d_6): δ 10.4 (s, 1H), 9.1 (s, 1H), 7.0-6.4 (m, 4H), 3.4-2.0 (m, 15H), 2.2 (s, 3H), 1.9 (s, 3H), 1.0 (t, 6H).
MS (TSP) m/z = 396.4 (MH^+)

EXAMPLE 13
(±)-trans-2-Benzylaminocarbonyl-3,6-dimethyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline

1 g (3.3 mmol) of (±)-trans-2-ethyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride, 2.95 g (10 mmol) of N-benzyl-2-phenylhydrazono-3-oxobutyramide, 0.82 g (10 mmol) of CH_3COONa, 2.6 g (40 mmol) of zinc dust and 5 ml of glacial acetic acid were treated as described in example 1. The residue was crystallised from AcOEt yielding 0.65 g of the title compound. M.p. = 162-164 °C.
$C_{28}H_{33}N_3O_2$
I.R. (KBr): 3350, 3220, 2920, 1640, 1630, 1510 cm^{-1}.

EXAMPLE 14
(±)-trans-2-Benzylaminocarbonyl-3,6-dimethyl-8a-(3-hydroxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

0.38 g of (±)-trans-2-benzylaminocarbonyl-3,6-dimethyl-8a-(3-methoxyphenyl)-

4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline were treated with 0.55 ml (5.7 mmol) of boron tribromide as described in example 2. The residue was dissolved in MeOH and the solution brought to acidic pH with HCl/Et_2O. The solvent was evaporated *in vacuo* and the solid crystallised from a mixture of acetone/MeOH = 1:1, yielding 0.15 g of the title compound. M.p. = 297-299 °C

$C_{27}H_{31}N_3O_2 \cdot HCl$

I.R. (KBr): 3290, 2910, 1650, 1540, 1320 cm^{-1}

EXAMPLE 15

(±)-trans-3,6-Dimethyl-8a-(3-methoxyphenyl)-2-pyrrolidinocarbonyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline

1 g (3.3 mmol) of (±)-trans-2-ethyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride, 2.6 g (10 mmol) of 1-(2-phenylhydrazono-3-oxobutyryl)pyrrolidine, 0.82 g (10 mmol) of CH_3COONa, 2.6 g (40 mmol) of zinc dust and 5 ml of glacial acetic acid were treated as described in example 1. The residue was purified by chromatography on silica gel (EtOAc/MeOH 0%→5%) then crystallised from a mixture of acetone/MeOH = 1:1 yielding 0.65 g of the title compound. M.p. = 171-173 °C.

$C_{25}H_{33}N_3O_2$

I.R. (KBr): 3280, 2940, 1610, 1580 cm^{-1}.

EXAMPLE 16

(±)-trans-3,6-Dimethyl-8a-(3-hydroxyphenyl)-2-pyrrolidinocarbonyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

0.38 g of (±)-trans-3,6-dimethyl-8a-(3-methoxyphenyl)-2-pyrrolidinocarbonyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline were treated with 0.55 ml (5.7 mmol) of boron tribromide as described in example 2. The residue was triturated in Et_2O and the solution brought to acidic pH with HCl/Et_2O. The solvent was evaporated *in vacuo* and the solid crystallised from a mixture of acetone/MeOH = 1:1, yielding 0.15 g of the title compound. M.p. = 230-233 °C

$C_{24}H_{31}N_3O_2 \cdot HCl$

I.R. (KBr): 3400, 3140, 1600, 1580, 1510 cm^{-1}

EXAMPLE 17

(±)-trans-6-Ethyl-3-methyl-8a-(3-methoxyphenyl)-2-phenylaminocarbonyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline

0.8 g (2.47 mmol) of (±)-trans-2-ethyl-4a-(3-methoxyphenyl)-6-oxo-

1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride, 0.7 g (2.47 mmol) of N-phenyl-2-phenylhydrazono-3-oxobutyramide, 0.24 g (3 mmol) of CH_3COONa, 0.74 g (11.3 mmol) of zinc dust and 2.5 ml of glacial acetic acid were treated as described in example 1. The residue was purified by flash chromatography (EtOAc/MeOH/conc. NH_4OH 90:10:1) yielding 0.28 g of the title compound. M.p. = 178-180 °C.

$C_{28}H_{33}N_3O_2$

I.R. (KBr): 3280, 2940, 1640, 1590 cm^{-1}.

N.M.R. 300 MHz ($CDCl_3$): δ 7.6-6.6 (m, 9H), 3.75 (s, 3H), 3.0-2.4 (m, 14H), 1.9 (q, 2H), 1.1 (t, 3H).

MS (TSP) m/z = 444.5 (MH^+)

EXAMPLE 18

(±)-trans-6-Ethyl-8a-(3-hydroxyphenyl)-3-methyl-2-phenylaminocarbonyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline

0.28 g of (±)-trans-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-2-phenylaminocarbonyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline were treated with 0.35 ml (1.9 mmol) of boron tribromide as described in example 2. The residue was purified by flash chromatography (EtOAc/MeOH/conc. NH_4OH 80:20:2) yielding 0.06 g of the title compound. M.p. = 271-272 °C.

$C_{27}H_{31}N_3O_2 \cdot HCl$

I.R. (KBr): 3310, 294, 1640, 1590 cm^{-1}

N.M.R. 300 MHz (DMSO-d_6): δ 10.6 (s, 1H), 9.2 (ds, 2H), 7.5-6.4 (m, 9H), 3.0-1.9 (m, 13H), 2.2 (s, 3H), 1.0 (t, 3H).

MS (TSP) m/z = 430.5 (MH^+)

EXAMPLE 19

(±)-trans-2-Diethylaminothiocarbonyl-6-ethyl-3-methyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline

1 g (2.4 mmol) of (±)-trans-2-diethylaminocarbonyl-6-ethyl-3-methyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline prepared as described in example 1 and 0.48 g (1.2 mmol) of Lawesson reagent (*Synthesis*, 941, 1979) were dissolved in 50 ml of toluene. The solution was refluxed for 6 h. The solvent was evaporated *in vacuo*. The residue was treated with s.s. K_2CO_3 and extracted with AcOEt. The organic layers were dried over Na_2SO_4 and then the solvent evaporated *in vacuo*. The crude product was purified by flash chromatography (AcOEt/MeOH/conc. NH_4OH 80:20:2) yielding 0.5 g of the title compound. M.p. =

156-158 °C.
$C_{26}H_{37}N_3OS$
I.R. (nujol): 1600, 1581, 1461, 1378 cm^{-1}.
N.M.R. 300 MHz ($CDCl_3$): δ 8.3 (s, 1H), 7.2-6.7 (m, 4H), 4.0-3.8 (m, 4H), 3.75 (s, 3H), 3.0-1.9 (m, 13H), 1.9 (s, 3H), 1.2 (t, 6H), 1.1(t, 3H).
MS (TSP) m/z = 440.6 (MH^+)

EXAMPLE 20

(±)-trans-2-Diethylaminothiocarbonyl-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline

0.5 g of (±)-trans-2-diethylaminothiocarbonyl-6-ethyl-3-methyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline were treated with 0.64 ml (6.8 mmol) of boron tribromide as described in example 2. The residue was purified by flash chromatography (EtOAc/MeOH/conc. NH_4OH 80:20:2) yielding 0.12 g of the title compound. M.p = 243-245 °C.
$C_{25}H_{35}N_3OS$
I.R. (KBr): 3200, 2900, 1580, 1480 cm^{-1}
N.M.R. 300 MHz (DMSO-d_6): δ 10.2 (s, 1H), 9.2 (s, 1H), 7.1-6.4 (m, 4H), 3.9-3.7 (m, 6H), 3.0-1.75 (m, H), 1.8 (s, 3H), 1.1 (t, 6H), 0.9 (t, 3H).
MS (TSP) m/z = 426.3 (MH^+)

EXAMPLE 21

(±)-trans-6-Cyclopropylmethyl-2-diethylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline hydrochloride

0.28 g (0.80 mmol) of (±)-trans-2-cyclopropylmethyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride, 0.56 g (2.14 mmol) of N,N-diethyl-2-phenylhydrazono-3-oxobutyramide, 0.131 g (1.6 mmol) of CH_3COONa, 0.402 g (6.16 mmol) of zinc dust and 10 ml of glacial acetic acid were treated as described in example 1. The residue was purified by flash chromatography ($(i\text{-}Pr)_2O$/MeOH/conc. NH_4OH 90:10:0.5). The product was dissolved in acetone and the solution brought to acidic pH with Et_2O/HCl. The solid was filtered, washed and dried yielding 0.225 g of the title compound. M.p. = 190-195 °C.
$C_{28}H_{39}N_3O_2 \cdot HCl$
I.R. (KBr): 3400, 3200, 2915, 2580, 1715, 1600 cm^{-1}
N.M.R. 300 MHz (DMSO-d_6): δ 10.3 (bs, 1H), 10.2 (s, 1H), 7.3-6.7 (m, 4H), 3.7 (s, 3H), 3.6-2.5 (m, 14H), 2.5 (s, 3H), 2.1-1.4 (m, 4H), 1.0 (t, 6H), 0.6 (m, 2H), 0.4 (m, 2H).

MS (EI) m/z = 450.5 (MH^+)

EXAMPLE 22

(±)-trans-6-Cyclopropylmethyl-2-diethylaminocarbonyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline hydrochloride

0.225 g (0.46 mmol) of (±)-trans-6-cyclopropylmethyl-2-diethylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline were treated with 0.26 ml (2.76 mmol) of boron tribromide as described in example 2. The residue was purified by flash chromatography ((i-$Pr)_2O$/MeOH/conc. NH_4OH 75:25:0.5). The crude product was dissolved in acetone and the solution brought to acidic pH with HCl/Et_2O. The precipitate was filtered yielding 0.07 g of the title compound. M.p. = 270-272 °C dec.

$C_{27}H_{37}N_3O_2 \cdot HCl$

I.R. (KBr): 3010, 2700, 1595, 1580 cm^{-1}

N.M.R. 300 MHz (DMSO-d_6): δ 10.4 (bs, 1H), 10.3 (s, 1H) 9.2 (s, 1H), 7.1-6.5 (m, 4H), 3.5-2.0 (m, 15H), 2.8 (s, 3H), 1.9 (s, 3H), 1.0 (t, 6H), 0.6 (m, 2H), 0.4 (m, 2H).

MS (EI) m/z(free base) = 435.3 (M^+)

EXAMPLE 23

(±)-trans-2-Diisopropylaminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline

0.7 g (2.2 mmol) of (±)-trans-2-ethyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride, 2.0 g (7.0 mmol) of N,N-diisopropyl-2-phenylhydrazono-3-oxobutyramide, 0.575 g (7.0 mmol) of CH_3COONa, 1.83 g (28.0 mmol) of zinc dust and 3.5 ml of glacial acetic acid were treated as described in example 1 yielding 1.0 g of the title compound as an oil.

$C_{28}H_{41}N_3O_2$

I.R. (neat) : 3250, 2960, 2580, 1740, 1600 cm^{-1}

N.M.R. 300 MHz (DMSO-d_6) (hydrochloride): δ 10.2 (s, 1H), 7.2-6.6 (m, 4H), 3.7 (s, 3H), 3.6-1.8 (m, 18H), 1.8 (s, 3H), 1.0 (d, 12H), .

MS (EI) m/z = 451.3 (M^+).

EXAMPLE 24

(±)-trans-2-Diisopropylaminocarbonyl-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

1.0 g (2.2 mmol) of (±)-trans-2-diisopropylaminocarbonyl-6-ethyl-8a-(3-

methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline were treated with 1.15 ml (12.0 mmol) of boron tribromide as described in example 2. The crude product was dissolved in MeOH and the solution brought to acidic pH with HCl/Et_2O. The solvent was evaporated *in vacuo* and the solid crystallized from acetone, yielding 0.5 g of the title compound. M.p. = 263-265 °C

$C_{27}H_{39}N_3O_2 \cdot HCl$

I.R. (KBr): 3110, 2960, 1720, 1595, cm^{-1}

N.M.R. 300 MHz (DMSO-d_6): δ 10.4 (s, 1H), 10.3 (bs, 1H), 9.2 (s, 1H), 7.1-6.5 (m, 4H), 3.7-2.0 (m, 18H), 1.8 (s, 3H), 1.0 (d, 12H) .

MS (EI) m/z = 437.3 (M^+).

EXAMPLE 25

(±)-trans-2-Aminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline

3.24 g (10 mmol) of (±)-trans-2-ethyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride, 6.16 g (30.0 mmol) of 2-phenylhydrazono-3-oxobutyramide, 2.46 g (7.0 mmol) of CH_3COONa, 7.85 g (120.0 mmol) of zinc dust and 15 ml of glacial acetic acid were treated as described in example 1. The residue was purified by chromatography on silica gel (Et_2O-EtOAc/MeOH 0%→50%) yielding 3.0 g of oily product which was triturated in Et_2O yielding 2.5 g of the title compound. M.p. = 176-178 °C

$C_{22}H_{29}N_3O_2$

I.R. (neat) : 3200, 2915, 2580, 1640, 1600, 1580 cm^{-1}

N.M.R. 300 MHz (DMSO-d_6) : δ 10.4 (s, 1H), 7.2-6.5 (m, 4H), 3.8 (s, 3H), 3.0-1.8 (m, 18H), 1.0 (t, 3H).

MS (EI) m/z = 368.1 (MH^+).

EXAMPLE 26

(±)-trans-2-Aminocarbonyl-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline hydrochloride

0.48 g (1.3 mmol) of (±)-trans-2-aminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline were treated with 0.75 ml (7.8 mmol) of boron tribromide as described in example 2. The crude product was purified by chromatography on silica gel (CH_2Cl_2/MeOH 20%→30%). The residue was dissolved in MeOH and the solution brought to acidic pH with HCl/Et_2O. The solvent was evaporated *in vacuo* and the solid crystallized from acetone/MeOH, yielding 0.13 g of the title compound. M.p. = 270-273 °C

$C_{21}H_{27}N_3O_2 \cdot HCl$
I.R. (KBr): 3160, 1645, 1595, 1450 cm^{-1}
N.M.R. 300 MHz (DMSO-d_6): δ 10.5 (s, 1H), 10.2 (bs, 1H), 7.2-6.5 (m, 4H), 3.7-2.0 (m, 16H), 2.0 (s, 3H), 1.2 (t, 3H) .
MS (EI) m/z = 354.1 (MH^+).

EXAMPLE 27

(±)-trans-6-Ethyl-2-ethoxycarbonyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-3-trifluoromethyl-1H-pyrrolo[2,3-g]isoquinoline

3.24 g (10 mmol) of (±)-trans-2-ethyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride, 8.65 g (30 mmol) of ethyl 2-phenylhydrazono-4,4,4-trifluoro-3-oxobutyrate, 2.46 g (30 mmol) of CH_3COONa, 7.85 g (120 mmol) of zinc dust and 15 ml of glacial acetic acid were treated as described in example 1. The residue was purified by chromatography on silica gel (EtOAc/MeOH 0%→10%) yielding 3.0 g of product which was triturated in Et_2O yielding 2.5 g of the title compound. M.p. 209-211 °C
$C_{24}H_{29}F_3N_2O_3$
I.R. (neat) : 3000, 1725, 1680, 1600 cm^{-1}
N.M.R. 300 MHz (DMSO-d_6) (hydrochloride): δ 12.0 (s, 1H), 7.2-6.6 (m, 4H), 4.2 (q, 2H), 3.8 (s, 3H), 3.6-1.8 (m, 13H), 1.2 (t, 3H), 1.0 (t, 3H) .
MS (EI) m/z = 451.1 (MH^+).

EXAMPLE 28

(±)-trans-6-Ethyl-2-ethoxycarbonyl-8a-(3-hydroxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-3-trifluoromethyl-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

0.6 g (1.3 mmol) of (±)-trans-6-ethyl-2-ethoxycarbonyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-3-trifluoromethyl-1H-pyrrolo[2,3-g]isoquinoline were treated with 0.75 ml (7.8 mmol) of boron tribromide as described in example 2. The crude product was purified by chromatography on silica gel (CH_2Cl_2/MeOH 20%→30%). The residue was dissolved in MeOH and the solution brought to acidic pH with HCl/Et_2O. The solvent was evaporated *in vacuo* and the solid was triturated in Et_2O, yielding 0.14 g of the title compound. M.p. = 275-278 °C
$C_{23}H_{27}F_3N_2O_3 \cdot HCl$
I.R. (KBr): 3160, 2680, 1705, 1600, cm^{-1}
N.M.R. 300 MHz (DMSO-d_6): δ 12.1 (s, 1H), 10.4 (bs, 1H), 9.3 (s, 1H), 7.2-6.5 (m, 4H), 4.2 (q, 2H), 3.7-2.2 (m, 10H), 2.0 (s, 3H), 1.2 (m, 6H) .
MS (EI) m/z = 436.1 (M^+).

EXAMPLE 29

(±)-trans-2-Diethylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-6-propyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

0.37 g (0.86 mmol) of (±)-trans-2-diethylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline hydrochloride, 0.11 g (0.90 mmol) of propyl bromide, 0.24 g (1.71 mmol) of potassium carbonate and a catalytic amount of potassium iodide were dissolved in 5 ml of dimethylformamide and heated to 80 °C for 2 h. The solvent was evaporated *in vacuo*, the residue was taken up in H_2O and extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4 and the solvent removed *in vacuo*. The residue was dissolved in Et_2O and the solution brought to acidic pH with HCl/Et_2O. The precipitate was filtered yielding 0.25 g of the title compound. M.p. = 102-106 °C dec.

$C_{27}H_{39}N_3O_2 \cdot HCl$

I.R. (KBr) : 3400, 3200, 2915, 2580, 1715, 1600 cm^{-1}

EXAMPLE 30

(±)-trans-2-Diethylaminocarbonyl-8a-(3-hydroxyphenyl)-3-methyl-6-propyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

0.25 g (0.53 mmol) of (±)-trans-2-diethylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-6-propyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline hydrochloride were treated with 0.3 ml (3.18 mmol) of boron tribromide as described in example 2. The crude product was dissolved in MeOH and the solution brought to acidic pH with HCl/Et_2O. The solvent was evaporated *in vacuo* and the solid crystallized from acetone, yielding 0.04 g of the title compound. M.p. = 236-238 °C.

$C_{26}H_{37}N_3O_2 \cdot HCl$

I.R. (KBr): 3130, 2915, 1590, 1460, cm^{-1}

N.M.R. 300 MHz (DMSO-d_6): δ 10.2 (s, 1H), 9.0 (s, 1H), 7.2-6.4 (m, 4H), 3.7-2.2 (m, 12H), 2.0 (s, 3H), 1.8 (m, 2H), 1.6 (m, 2H), 1.0 (t, 6H), 0.8 (t, 6H) .

MS (EI) m/z = 423.2 (M^+).

EXAMPLE 31

(±)-trans-2-Dimethylaminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline

1.0 g (3.1 mmol) of (±)-trans-2-ethyl-4a-(3-methoxyphenyl)-6-oxo-

1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride, 2.33 g (10 mmol) of N,N-dimethyl-2-phenylhydrazono-3-oxobutyramide, 0.82 g (10 mmol) of CH_3COONa, 2.6 g (40 mmol) of zinc dust and 5 ml of glacial acetic acid were treated as described in example 1. The residue was purified by chromatography on silica gel (EtOAc/MeOH 0%→30%) yielding 0.5 g of product which was crystallized from Et_2O yielding 0.5 g of the title compound. M.p. = 151-153 °C

$C_{24}H_{33}N_3O_2$

I.R. (neat) : 3210, 2910, 1585 cm^{-1}

N.M.R. 300 MHz (DMSO-d_6) (hydrochloride): δ 10.3 (s, 1H), 7.2-6.6 (m, 4H), 3.8 (s, 3H), 3.6-1.8 (m, 22H), 1.0 (t, 3H) .

MS (EI) m/z = 395.2 (M^+).

EXAMPLE 32

(±)-trans-2-Dimethylaminocarbonyl-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

0.5 g (1.25 mmol) of (±)-trans-2-dimethylaminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline were treated with 0.725 ml (7.5 mmol) of boron tribromide as described in example 2. The crude product was dissolved in MeOH and the solution brought to acidic pH with HCl/Et_2O. The solvent was evaporated *in vacuo* and the solid crystallized from EtOH, yielding 0.15 g of the title compound. M.p. = 305 °C dec.

$C_{23}H_{31}N_3O_2 \cdot HCl$

I.R. (KBr): 3160, 1600, 1580 cm^{-1}

N.M.R. 300 MHz (DMSO-d_6): δ 10.4 (s, 1H), 10.2 (bs, 1H), 9.3 (s, 1H), 7.2-6.5 (m, 4H), 3.7-2.0 (m, 22H), 1.2 (t, 3H) .

MS (TSP) m/z = 382.0 (M^+).

EXAMPLE 33

(-)-trans-2-Diethylaminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

1.9 g (5.87 mmol) of (-)-trans-2-ethyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride (Int. Pat. Appl. WO 93/01186), 4.61 g (17.61 mmol) of N,N-diethyl-2-phenylhydrazono-3-oxobutyramide, 1.45 g (17.61 mmol) of CH_3COONa, 1.9 g (29.35 mmol) of zinc dust and 15 ml of glacial acetic acid were treated as described in example 1. The residue was purified by flash chromatography ((i-Pr)$_2$O/MeOH/conc. NH_4OH 75:25:0.5). The resulting solid was dissolved in acetone and the solution brought to

acidic pH with HCl/Et_2O. The solvent was evaporated *in vacuo* and the solid triturated with Et_2O, yielding 2.3 g of the title compound. M.p. = 201-205 °C.
$C_{26}H_{37}N_3O_2 \cdot HCl$
I.R. (KBr) : 3400, 3200, 2920, 1600 cm^{-1}
N.M.R. 300 MHz (DMSO-d_6) : δ 10.7 (bs, 1H), 10.4 (s, 1H), 7.3-6.7 (m, 4H), 3.7 (s, 3H), 3.6-2.5 (m, 17H), 1.8 (s, 3H), 1.2-1.0 (m, 9H)
$[\alpha]^{20}_D$ = -20.32 (c = 1, MeOH).

The I.R. and N.M.R. spectra were identical to those obtained for the racemate.

EXAMPLE 34
(-)-trans-2-Diethylaminocarbonyl-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

2.3 g (5.0 mmol) of (-)-trans-2-diethylaminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride were treated with 2.9 ml (30 mmol) of boron tribromide as described in example 2. The crude product was dissolved in MeOH and the solution brought to acidic pH with HCl/Et_2O. The precipitate was filtered and crystallized from a mixture of acetone/MeOH = 9/1, yielding 0.37g of the title compound. M.p.= 239-241°C.
$C_{25}H_{35}N_3O_2 \cdot HCl$
I.R. (KBr) : 3200, 2980, 2940, 1600 cm^{-1}
N.M.R. 300 MHz (DMSO-d_6) : δ 10.4 (s, 1H), 7.3-6.7 (m, 4H), 3.6-2.5 (m, 17H), 1.8 (s, 3H), 1.2-1.0 (m, 9H)
MS (EI) m/z = 409.3 (M^+).
$[\alpha]^{20}_D$ = -57.94 (c = 1, MeOH).

The I.R. and N.M.R. spectra were identical to those obtained for the racemate.

EXAMPLE 35
(+)-trans-2-Diethylaminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

1.9 g (5.87 mmol) of (+)-trans-2-ethyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride (Int. Pat. Appl. WO 93/01186), 4.61 g (17.61 mmol) of N,N-diethyl-2-phenylhydrazono-3-oxobutyramide, 1.45 g (17.61 mmol) of CH_3COONa, 1.9 g (29.35 mmol) of zinc dust and 15 ml of glacial acetic acid were treated as described in example 1. The residue was purified by flash chromatography ((i-Pr)$_2$O/MeOH/conc. NH_4OH

75:25:0.5). The resulting solid was dissolved in acetone and the solution brought to acidic pH with HCl/Et_2O. The solvent was evaporated *in vacuo* and the solid triturated with Et_2O, yielding 2.0 g of the title compound. M.p. = 200-204 °C

$C_{26}H_{37}N_3O_2 \cdot HCl$

I.R. (KBr) : 3400, 3200, 2920, 1600 cm^{-1}

N.M.R. 300 MHz (DMSO-d_6) : δ 10.7 (bs, 1H), 10.4 (s, 1H), 7.3-6.7 (m, 4H), 3.7 (s, 3H), 3.6-2.5 (m, 17H), 1.8 (s, 3H), 1.2-1.0 (m, 9H)

$[\alpha]^{20}_D$ = +20.65 (c = 1, MeOH).

The I.R. and N.M.R. spectra were identical to those obtained for the racemate.

EXAMPLE 36

(+)-trans-2-Diethylaminocarbonyl-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

2.0 g (4.3 mmol) of (+)-trans-2-diethylaminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride were treated with 2.5 ml (25.8 mmol) of boron tribromide as described in example 2. The crude product was dissolved in MeOH and the solution brought to acidic pH with HCl/Et_2O. The precipitate was filtered and crystallized from a mixture of acetone/MeOH = 9/1, yielding 0.28 g of the title compound. M.p. = 239-240 °C.

$C_{25}H_{35}N_3O_2 \cdot HCl$

I.R. (KBr) : 3200, 2980, 2940, 1600 cm^{-1}

N.M.R. 300 MHz (DMSO-d_6) : δ 10.6 (bs, 1H), 10.4 (s, 1H), 7.3-6.7 (m, 4H), 3.6-2.5 (m, 17H), 1.8 (s, 3H), 1.2-1.0 (m, 9H)

MS (EI) m/z = 409.2 (M^+).

$[\alpha]^{20}_D$ = +57.49 (c = 1, MeOH).

The I.R. and N.M.R. spectra were identical to those obtained for the racemate.

EXAMPLE 37

(±)-trans-2-Diethylaminocarbonyl-6-(2-furylmethyl)-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline hydrochloride

1.3 g (3.3 mmol) of (±)-trans-2-diethylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline, 0.28 ml (4.95 mmol) of acetic acid, 0.33 ml (3.96 mmol) of 2-furaldehyde were dissolved in 50 ml of MeOH under nitrogen atmosphere. 0.415 g (6.6 mmol) of sodium cyanoborohydride were added and the solution stirred for 15 h. Additional acetic acid

(0.1 ml), 2-furaldehyde (0.3 ml) and sodium cyanoborohydride (0.2 g) were added. After two hours of stirring the reaction mixture was cooled to 0 °C and 50 ml of 5N hydrochloric acid were added. The solvent was removed *in vacuo*, the aqueous solution was extracted with Et_2O, the pH was adjusted to 8 with 20% NaOH and then extracted with AcOEt. The organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was dissolved in acetone/MeOH and the solution brought to acidic pH with HCl/Et_2O. The precipitate was filtered, yielding 1.7 g of the title compound. M.p. = 105 °C dec.

$C_{29}H_{37}N_3O_3 \cdot HCl$

I.R. (KBr) : 3400, 3200, 2940, 1600 cm^{-1}

N.M.R. 300 MHz (DMSO-d_6) : δ 10.4 (s, 1H), 7.8-6.4 (m, 7H), 4.2 (s, 2H), 3.8 (s, 3H), 3.6-1.8 (m, 18H), 1.2-1.0 (m, 6H)

MS (EI) m/z = 475 (M^+).

EXAMPLE 38

(±)-trans-2-Diethylaminocarbonyl-6-(2-furylmethyl)-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline

1.7 g (3.32 mmol) of (±)-trans-2-dimethylaminocarbonyl-6-(2-furylmethyl)-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline hydrochloride were treated with 1.86 ml (19.9 mmol) of boron tribromide as described in example 2. The residue was purified by flash chromatography (EtOAc/MeOH/conc.NH_4OH 95:5:0.5). The solid was triturated with acetone, yielding 0.07 g of the title compound. M.p. = 215-216 °C dec.

$C_{28}H_{35}N_3O_3$

I.R. (KBr): 3340, 2930, 2900, 1590 cm^{-1}

N.M.R. 300 MHz (DMSO-d_6): δ 10.4 (s, 1H), 9.2 (s, 1H), 7.5 (s, 2H), 7.1-6.2 (m, 6H), 3.5-1.8 (m, 19H), 1.0 (t, 6H).

MS (EI) m/z = 461.1 (M^+).

EXAMPLE 39

(±)-trans-2-Diethylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline

1.6 g (5.7 mmol) of (±)-trans-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride, 6.0 g (22.8 mmol) of N,N-diethyl-2-phenylhydrazono-3-oxobutyramide, 1.9 g (22.8 mmol) of CH_3COONa, 2.2 g (34.2 mmol) of zinc dust and 30 ml of glacial acetic acid were treated as described in example 1, yielding 1.3 g of the title compound. M.p. = 197-199 °C .

$C_{24}H_{33}N_3O_2$
I.R. (KBr) : 3270, 2915, 1605 cm^{-1}

EXAMPLE 40

(±)-trans-6-Butyl-2-diethylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline

0.2 g (0.57 mmol) of (±)-trans-2-butyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride, 0.45 g (1.71 mmol) of N,N-diethyl-2-phenylhydrazono-3-oxobutyramide, 0.14 g (1.71 mmol) of CH_3COONa, 0.22 g (3.42 mmol) of zinc dust and 5 ml of glacial acetic acid were treated as described in example 1, yielding 0.15 g of the title compound. M.p. = 134 °C dec.

$C_{28}H_{41}N_3O_2$
I.R. (KBr) (hydrochloride) : 3200, 2960, 2925, 1630, 1600 cm^{-1}

EXAMPLE 41

(±)-trans-6-Butyl-2-diethylaminocarbonyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline

0.15 g (0.31 mmol) of (±)-trans-6-butyl-2-diethylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline were treated with 0.174 ml (1.86 mmol) of boron tribromide as described in example 2, yielding 0.06 g of the title compound. M.p. = 228-229 °C

$C_{27}H_{39}N_3O_2$
I.R. (KBr): 3330, 2920, 1590 cm^{-1}

EXAMPLE 42

(±)-trans-7-Ethyl-4a-(3-methoxyphenyl)-1-methyl-4,4a,5,6,7,8,8a,9-octahydro-2-phenyl-1H-imidazo[4,5-g]isoquinoline

A solution of 0.46 g (2.98 mmol) of N-methylbenzimidoyl chloride (*J. Am. Chem. Soc.*, 1962, 84, 769) in 12 ml of THF was cooled to -78 °C under nitrogen atmosphere and 0.73 ml (5.21 mmol) of triethylamine were added. After 30 min a solution of 0.45 g (1.49 mmol) of (±)-trans-2-ethyl-6-hydroxyimino-4a-(3-methoxyphenyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline in 3 ml of THF was added. The reaction mixture was allowed to warm to room temperature and then refluxed for 5 h. Water was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine and dried. The solvent was removed *in vacuo*

and the resulting product was dissolved in 25 ml of toluene, 0.99 g of p-toluenesulphonic acid were added and the reaction mixture was heated to reflux in a Dean-Stark apparatus for 6 h. The solvent was removed *in vacuo*, the residue was taken up in water, the pH adjusted to 10 with 1N NaOH. The aqueous layer was extracted with CH_2Cl_2, the organic layer was dried and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (EtOAc/MeOH/conc.NH_4OH 85:15:2) yielding 0.276 g of the title compound. M.p. = 146-150 °C.

$C_{26}H_{31}N_3O$

I.R. (KBr): 2920, 1600, 1580 cm^{-1}

N.M.R. 300 MHz (DMSO-d_6): δ 7.6-6.6 (m, 9H), 3.8 (s, 3H), 3.5 (s, 3H), 3.0-1.6 (m, 13H), 1.0 (t, 3H).

MS (EI) m/z = 401.2 (M^+).

EXAMPLE 43

(±)-trans-7-Ethyl-4a-(3-hydroxyphenyl)-1-methyl-4,4a,5,6,7,8,8a,9-octahydro-2-phenyl-1H-imidazo[4,5-g]isoquinoline

0.27 g (0.67 mmol) of (±)-trans-7-ethyl-4a-(3-methoxyphenyl)-1-methyl-4,4a,5,6,7,8,8a,9-octahydro-2-phenyl-1H-imidazo[4,5-g]isoquinoline were treated with 0.38 ml (4.02 mmol) of boron tribromide as described in example 2. The residue was purified by flash chromatography (EtOAc/MeOH/conc.NH_4OH 80:20:2). The resulting solid was crystallized from acetone, yielding 0.13 g of the title compound. M.p. = 249-251 °C.

$C_{25}H_{29}N_3O$

I.R. (KBr): 3400, 2940, 1595, 1450 cm^{-1}

N.M.R. 300 MHz (DMSO-d_6): δ 9.1 (s, 1H), 7.8-6.4 (m, 9H), 3.5 (s, 3H), 3.0-1.6 (m, 13H), 1.0 (t, 3H).

MS (EI) m/z = 387.2 (M^+).

EXAMPLE 44

(±)-trans-6-Ethyl-8a-(3-methoxyphenyl)-3-methyl-2-pyrrolidinocarbonyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

1 g (3.1 mmol) of (±)-trans-2-ethyl-4a-(3-methoxyphenyl)-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline hydrochloride, 2.4 g (9.3 mmol) of 1-(2-phenylhydrazono-3-oxobutyryl)pyrrolidine, 0.76 g (9.3 mmol) of CH_3COONa, 2.4 g (37.2 mmol) of zinc dust and 10 ml of glacial acetic acid were treated as described in example 1. The crude product was purified by flash chromatography

(EtOAc/MeOH/conc.NH_4OH 80:20:0.5). The residue was dissolved in acetone and the solution brought to acidic pH with HCl/Et_2O. The precipitate was filtered, yielding 0.63 g of the title compound. M.p. = 127-131 °C.

$C_{26}H_{35}N_3O_2 \cdot HCl$

I.R. (KBr): 3280, 2940, 1610, 1580 cm^{-1}.

EXAMPLE 45

(±)-trans-6-Ethyl-8a-(3-hydroxyphenyl)-3-methyl-2-pyrrolidinocarbonyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline

0.63 g (1.37 mmol) of (±)-trans-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-2-pyrrolidinocarbonyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline were treated with 0.77 ml (8.22 mmol) of boron tribromide as described in example 2. The residue was purified by flash chromatography (EtOAc/MeOH/conc.NH_4OH 80:20:0.5). The resulting solid was triturated with Et_2O, yielding 0.13 g of the title compound. M.p. = 224-226 °C.

$C_{25}H_{33}N_3O_2$

I.R. (KBr): 3400, 2940, 1595, 1450 cm^{-1}

EXAMPLE 46

(±)-trans-2-Diisopropylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-6-propyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

0.34 g (0.74 mmol) of (±)-trans-2-diisopropylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline hydrochloride, 0.095 g (0.78 mmol) of propyl bromide, 0.204 g (1.48 mmol) of potassium carbonate and a catalytic amount of potassium iodide in 5 ml of dimethylformamide were treated as described in example 29. The residue was dissolved in Et_2O and the solution brought to acidic pH with HCl/Et_2O. The precipitate was filtered yielding 0.22 g of the title compound. M.p. = 150 °C dec.

$C_{29}H_{43}N_3O_2 \cdot HCl$

I.R. (KBr) : 3400, 3200, 2915, 2580, 1600 cm^{-1}

EXAMPLE 47

(±)-trans-2-Diisopropylaminocarbonyl-8a-(3-hydroxyphenyl)-3-methyl-6-propyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride

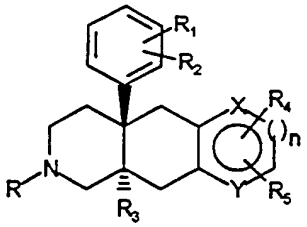
0.22 g (0.44 mmol) of (±)-trans-2-diisopropylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-6-propyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline

hydrochloride were treated with 0.25 ml (2.64 mmol) of boron tribromide as described in example 2. The residue was purified by flash chromatography (EtOAc/MeOH/conc.NH_4OH 80:20:0.5). The residue was dissolved in acetone and the solution brought to acidic pH with HCl/Et_2O. The precipitate was filtered yielding 0.055 g of the title compound. M.p. = 240-243 °C.

$C_{28}H_{41}N_3O_2 \cdot HCl$

I.R. (KBr): 3400, 2940, 1595, 1450 cm^{-1}

CHEMICAL TABLE



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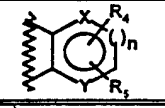
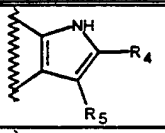
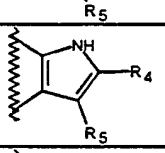
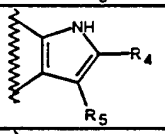
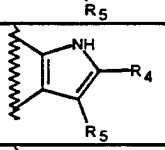
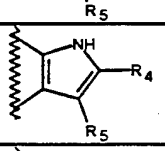
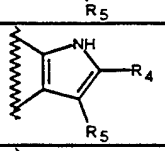
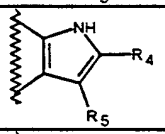
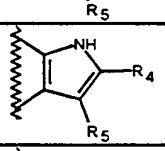
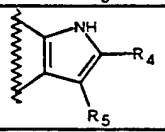
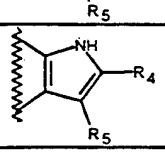
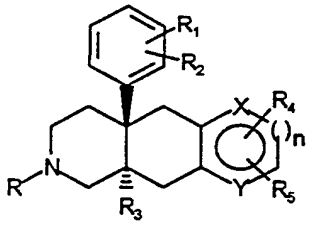
Ex. n.	R	R_1	R_2	R_3	R_4	R_5		*	Molecular formula	M.P. °C
1	Et	m-OMe	H	H	$CONEt_2$	Me		(±)	$C_{26}H_{37}N_3O_2$	247 dec. (as ·HCl)
2	Et	m-OH	H	H	$CONEt_2$	Me		(±)	$C_{25}H_{35}N_3O_2$	221-223
3	Et	m-OMe	H	H	COOEt	Me		(±)	$C_{24}H_{32}N_2O_3$	-------
4	Et	m-OH	H	H	COOEt	Me		(±)	$C_{23}H_{30}N_2O_3.0.5\ H_2O$	195-197
5	Et	m-OMe	H	H	CON-n-Pr_2	Me		(±)	$C_{28}H_{41}N_3O_2$·HCl	250 dec.
6	Et	m-OH	H	H	CON-n-Pr_2	Me		(±)	$C_{27}H_{39}N_3O_2$	151-153
7	Et	m-OMe	H	H	COO-i-Bu	Me		(±)	$C_{26}H_{36}N_2O_3$·HCl	230 dec.
8	Et	m-OH	H	H	COOi-Bu	Me		(±)	$C_{25}H_{34}N_2O_3$	196-198
9	Me	m-OMe	H	H	$CONEt_2$	Me		(±)	$C_{25}H_{35}N_3O_2$	250 dec. (as ·HCl)
10	Me	m-OH	H	H	$CONEt_2$	Me		(±)	$C_{24}H_{33}N_3O_2$·HCl	>250

CHEMICAL TABLE (continued)



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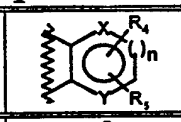
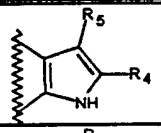
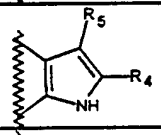
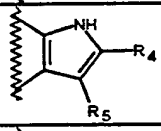
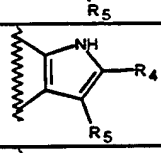
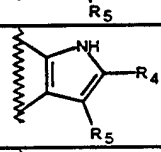
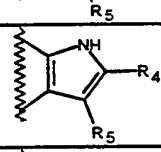
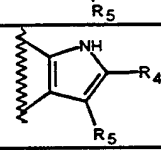
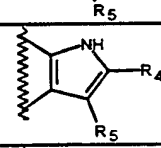
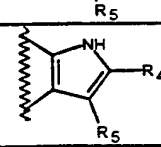
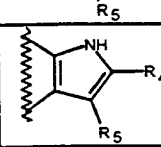
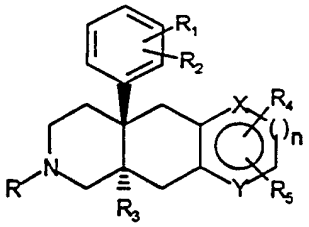
Ex. n.	R	R1	R2	R3	R4	R5		*	Molecular formula	M.P. °C
11	Me	m-OMe	H	H	$CONEt_2$	Me		(±)	$C_{25}H_{35}N_3O_2$	153-155
12	Me	m-OH	H	H	$CONEt_2$	Me		(±)	$C_{24}H_{33}N_3O_2$	235-238
13	Me	m-OMe	H	H	$CONHCH_2Ph$	Me		(±)	$C_{28}H_{33}N_3O_2$	162-164
14	Me	m-OH	H	H	$CONHCH_2Ph$	Me		(±)	$C_{27}H_{31}N_3O_2 \cdot HCl$	297-299
15	Me	m-OMe	H	H	$CON(-CH_2-)_4$	Me		(±)	$C_{25}H_{33}N_3O_2$	171-173
16	Me	m-OH	H	H	$CON(-CH_2-)_4$	Me		(±)	$C_{24}H_{31}N_3O_2 \cdot HCl$	230-233
17	Et	m-OMe	H	H	CONHPh	Me		(±)	$C_{28}H_{33}N_3O_2$	178-180
18	Et	m-OH	H	H	CONHPh	Me		(±)	$C_{27}H_{31}N_3O_2 \cdot HCl$	271-272
19	Et	m-OMe	H	H	$CSNEt_2$	Me		(±)	$C_{26}H_{37}N_3OS$	156-158
20	Et	m-OH	H	H	$CSNEt_2$	Me		(±)	$C_{25}H_{35}N_3OS$	243-245

CHEMICAL TABLE (continued)



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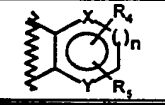
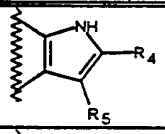
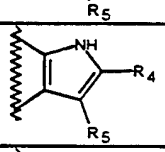
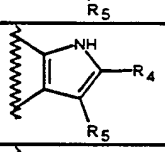
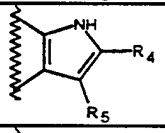
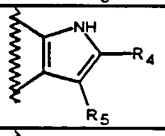
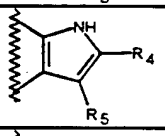
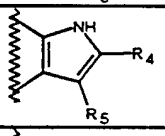
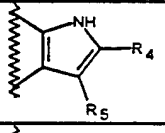
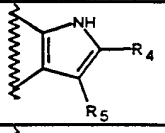
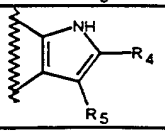
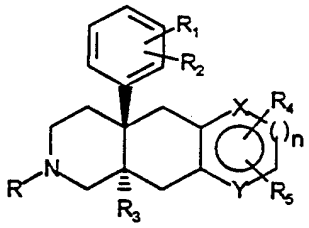
Ex. n.	R	R_1	R_2	R_3	R_4	R_5		*	Molecular formula	M.P. °C
21	CPM	m-OMe	H	H	$CONEt_2$	Me		(±)	$C_{28}H_{39}N_3O_2 \cdot HCl$	190-195
22	CPM	m-OH	H	H	$CONEt_2$	Me		(±)	$C_{27}H_{37}N_3O_2 \cdot HCl$	270-272 dec
23	Et	m-OMe	H	H	$CON(i\text{-}Pr)_2$	Me		(±)	$C_{28}H_{41}N_3O_2$	oil
24	Et	m-OH	H	H	$CON(i\text{-}Pr)_2$	Me		(±)	$C_{27}H_{39}N_3O_2 \cdot HCl$	263-265
25	Et	m-OMe	H	H	$CONH_2$	Me		(±)	$C_{22}H_{29}N_3O_2$	176-178
26	Et	m-OH	H	H	$CONH_2$	Me		(±)	$C_{21}H_{27}N_3O_2 \cdot HCl$	270-273
27	Et	m-OMe	H	H	COOEt	CF_3		(±)	$C_{24}H_{29}F_3N_2O_3$	209-211
28	Et	m-OH	H	H	COOEt	CF_3		(±)	$C_{23}H_{27}F_3N_2O_3 \cdot HCl$	275-278
29	n-Pr	m-OMe	H	H	$CONEt_2$	Me		(±)	$C_{27}H_{39}N_3O_2 \cdot HCl$	102-106 dec.
30	n-Pr	m-OH	H	H	$CONEt_2$	Me		(±)	$C_{26}H_{37}N_3O_2 \cdot HCl$	236-238

CHEMICAL TABLE (continued)



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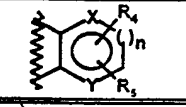
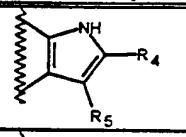
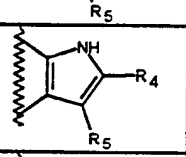
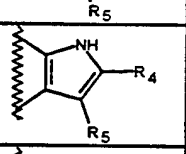
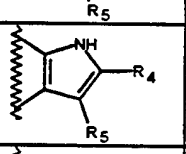
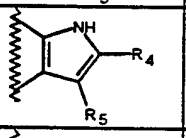
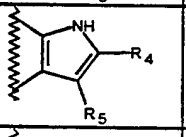
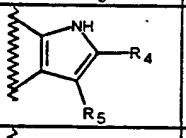
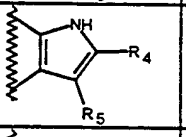
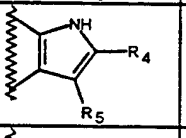
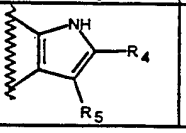
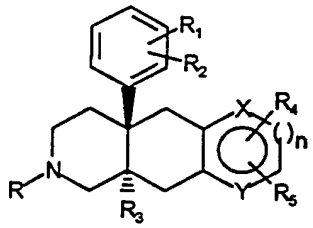
Ex. n.	R	R_1	R_2	R_3	R_4	R_5		*	Molecular formula	M.P. °C
31	Et	m-OMe	H	H	$CONMe_2$	Me		(±)	$C_{24}H_{33}N_3O_2$	151-153
32	Et	m-OH	H	H	$CONMe_2$	Me		(±)	$C_{23}H_{31}N_3O_2 \cdot HCl$	305 dec.
33	Et	m-OMe	H	H	$CONEt_2$	Me		(-)	$C_{26}H_{37}N_3O_2 \cdot HCl$	201-205
34	Et	m-OH	H	H	$CONEt_2$	Me		(-)	$C_{25}H_{35}N_3O_2 \cdot HCl$	239-241
35	Et	m-OMe	H	H	$CONEt_2$	Me		(+)	$C_{26}H_{37}N_3O_2 \cdot HCl$	200-204
36	Et	m-OH	H	H	$CONEt_2$	Me		(+)	$C_{25}H_{35}N_3O_2 \cdot HCl$	239-240
37	2-furyl methyl	m-OMe	H	H	$CONEt_2$	Me		(±)	$C_{29}H_{37}N_3O_3 \cdot HCl$	105 dec.
38	2-furyl methyl	m-OH	H	H	$CONEt_2$	Me		(±)	$C_{28}H_{35}N_3O_3$	215-216 dec.
39	H	m-OMe	H	H	$CONEt_2$	Me		(±)	$C_{24}H_{33}N_3O_2$	197-199
40	n-Bu	m-OMe	H	H	$CONEt_2$	Me		(±)	$C_{28}H_{41}N_3O_2$	134 dec.

CHEMICAL TABLE (continued)



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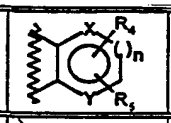
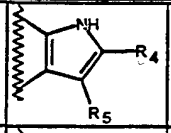
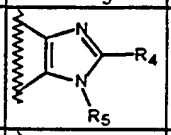
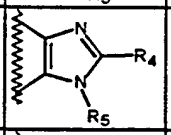
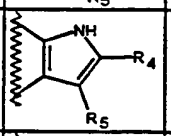
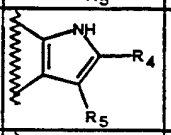
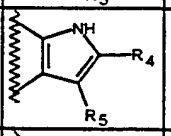
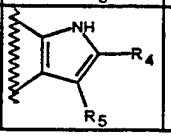
Ex. n.	R	R_1	R_2	R_3	R_4	R_5		*	Molecular formula	M.P. °C
41	n-Bu	m-OH	H	H	$CONEt_2$	Me		(±)	$C_{27}H_{39}N_3O_2$	228-229
42	Et	m-OMe	H	H	Ph	Me		(±)	$C_{26}H_{31}N_3O$	146-150
43	Et	m-OH	H	H	Ph	Me		(±)	$C_{25}H_{29}N_3O$	249-251
44	Et	m-OMe	H	H	$CON(-CH_2-)_4$	Me		(±)	$C_{26}H_{35}N_3O_2 \cdot HCl$	127-131
45	Et	m-OH	H	H	$CON(-CH_2-)_4$	Me		(±)	$C_{25}H_{33}N_3O_2$	224-226
46	n-Pr	m-OMe	H	H	$CON(i\text{-}Pr)_2$	Me		(±)	$C_{29}H_{43}N_3O_2 \cdot HCl$	150 dec.
47	n-Pr	m-OH	H	H	$CON(i\text{-}Pr)_2$	Me		(±)	$C_{28}H_{41}N_3O_2 \cdot HCl$	240-243

PHARMACOLOGICAL METHODS AND RESULTS

OPIOID RADIOLIGAND BINDING ASSAYS

Mouse brain membranes were prepared as described by Kosterlitz (*Br. J. Pharmacol.*, 1981, 73, 939.). The binding of the preferential *delta* ligand [^{3}H]-[D-Ala^2,D-Leu^5]-enkephalin (DADLE) was evaluated at its K_D concentration (1.3 nM) in presence of 40 nM of the unlabelled *mu* ligand [D-Ala^2, MePhe^4, Gly-ol^5]-enkephalin (DAMGO). The binding of the *mu* ligand [^{3}H]-DAMGO (*Eur. J. Pharmacol.*, 1989, 166, 213) and of the *kappa* ligand [^{3}H]-U69593 (*Excerpta Medica*, 1990, 211) were carried out at 0.5 nM. The non-specific binding was determined in presence of naloxone (10 μM) for all tritiated ligands. Binding data were expressed as percentage of inhibition and fitted the following equation: $f(x) = 100 \cdot X/(IC_{50} + X)$ where X are cold drug concentration values. The IC_{50} obtained were used to calculate the inhibitory constants (K_i) accordingly to the Cheng and Prusoff relation (*Biochem. Pharmacol.*, 1973, 22, 3099).

MOUSE VAS DEFERENS (MVD) BIOASSAYS

Vasa deferentia were obtained from CD-1 mice and were suspended in a Mg^{2+}-free Krebs buffer at 37 °C. For the *delta* agonist/antagonist studies, the tissues were electrically stimulated with pulse trains having the following parameters: train duration 50 ms, stimulus duration 2 ms, frequency of stimuli 50 Hz, maximal voltage 60-70 V, train frequency 0.1 Hz. Concentration response curves for each compounds were constructed cumulatively. Linear regression analysis and IC_{50} concentrations were evaluated according to Tallarida and Murray (*Manual of Pharmacological Calculations*, Springer Verlag NY, 1981).

The most potent compounds described in the present invention showed affinities for the *delta* receptor ranging from 0.5 to 200 nM with *delta* selectivity ranging from 30 to 1500 times in respect to the other opioid receptor types. These compounds displayed also potent *delta* agonist and antagonist properties in the MVD preparation. Selective *delta* agonists (antagonised by the selective *delta* antagonist naltrindole) displayed IC_{50}s ranging from 1 to 500 nM. For example, compound of example 34 shows a Ki *delta* = 0.73 nM, Ki *mu*/Ki *delta* = 110 and Ki *kappa*/Ki *delta* = 1105 and an IC_{50} = 26 nM in the MVD preparation.

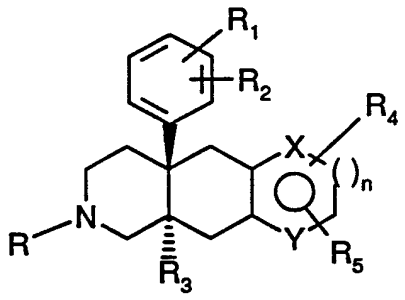
Selective *delta* antagonists showed K_es against DADLE ranging from 1 to 50 nM. For example, compound of example 10 shows a Ki *delta* = 2.15 nM, Ki *mu*/Ki *delta* = 45 and Ki *kappa*/Ki *delta* = 403 and a K_e = 7 nM against DADLE in the MVD preparation.

Mouse abdominal constriction (MAC) (*Proc. Soc. Exp. Biol. Med.*, 1957, 95, 729),

mouse tail-flick (MTF) (*J. Pharm. Exp. Ther.*, 1941, 72, 74) and mouse tail-flick warm water (MTF-WW) (*Life Sci.*, 1986, 39, 1795) were adopted to evaluate the antinociceptive efficacy of the compounds of the present invention.

Claims:

1. A compound, or solvate or salt thereof, of formula (I):



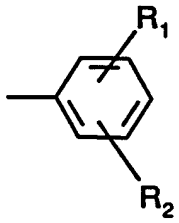
(I)

wherein:

R is hydrogen or a straight or branched C_1-C_5 alkyl, C_3-C_7 cycloalkyl, C_4-C_6 cycloalkylalkyl, C_3-C_5 alkenyl, aryl, aralkyl or furan-2-yl-alkyl;

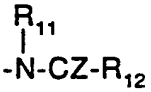
R_1 and R_2, which can be the same or different, are each hydrogen, hydroxy, C_1-C_3 alkoxy, halogen, SH, C_1-C_4-alkylthio, NHR_6, NR_6R_7, $NHCOR_6$, $NHSO_2R_6$, wherein R_6 and R_7, which are the same or different, are hydrogen or C_1-C_6 alkyl;

R_3 is hydrogen, hydroxy or C_1-C_3 alkoxy;

R_4 is a  group

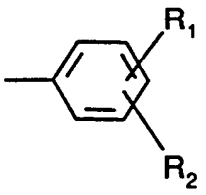
(R_1 and R_2 having the meanings defined above) or a -C(Z)-R_8 group, in which Z is oxygen or sulphur, and R_8 is C_1-C_{18}-alkyl, C_1-C_{18}-alkoxy or NR_9R_{10}, wherein R_9 and R_{10}, which may be the same or different, are hydrogen, straight or branched C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_4-C_6 cycloalkylalkyl, C_3-C_6 alkenyl, aryl, aralkyl or an optionally substituted heterocyclic ring or, taken together with the nitrogen atom which they are linked to, they form an alkylene chain having from 2 to 5 carbon atoms, optionally interrupted by an oxygen or nitrogen atom;

or R_4 is a group



in which R_{11} and R_{12} are the same as R_9 and R_{10} respectively, and Z is as defined above;

R_5 is hydrogen, C_1-C_{18} alkyl, C_2-C_{18} alkenyl, trifluoromethyl or is a



group

(R_1 and R_2 having the meanings defined above);
n is zero or 1;
if n is zero, one of X or Y is NH, oxygen or sulphur, and the other is NH, CH or a R_4- or R_5-substituted carbon atom; if n is 1, then X and Y are both nitrogen, or one of them is nitrogen and the other is CH or a R_4- or R_5-substituted carbon atom.

2. A compound according to claim 1 in which R is methyl, ethyl, cyclopropylmethyl, propyl, 2-phenylethyl or 2-furylmethyl.

3. A compound according to claim 1 or 2 in which each of R_1 and R_2 is hydrogen, hydroxy, methoxy, chlorine, bromine, fluorine, SH, methylthio, amino, methylamino, ethylamino, dimethylamino, diethylamino, diisopropylamino, methylisopropylamino, acetylamino or sulfonylamino, at any position of the ring.

4. A compound according to any one of claims 1 to 3 in which R_5 is hydrogen, methyl, ethyl, propyl, butyl, hexyl, octyl, decyl, dodecyl, octadecyl, allyl, trifluoromethyl or phenyl.

5. A compound according to any one of claims 1 to 4 in which R_4 is ethoxycarbonyl, i-butyloxycarbonyl, aminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, di-n-propylaminocarbonyl, di-i-propylaminocarbonyl, pyrrolidinocarbonyl, benzylaminocarbonyl, phenylaminocarbonyl, morpholinocarbonyl, N-ethyl-N-i-isopropylaminocarbonyl, diethylaminothiocarbonyl, or phenyl.

6. A compound selected from:

(±)-trans-2-Diethylaminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline;

(±)-trans-2-Diethylaminocarbonyl-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline;

(±)-trans-6-Ethyl-2-ethoxycarbonyl-3-methyl-8a-(3-methoxyphenyl)-

4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline;

(±)-trans-6-Ethyl-2-ethoxycarbonyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline;

(±)-trans-Dipropylaminocarbonyl-6-ethyl-3-methyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride;

(±)-trans-Dipropylaminocarbonyl-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline;

(±)-trans-2-(*i*-Butoxycarbonyl)-6-ethyl-3-methyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride;

(±)-trans-2-(*i*-Butoxycarbonyl)-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride;

(±)-trans-2-Diethylaminocarbonyl-3,6-dimethyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline;

(±)-trans-2-Diethylaminocarbonyl-3,6-dimethyl-8a-(3-hydroxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride;

(±)-trans-2-Diethylaminocarbonyl-3,7-dimethyl-4a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[3,2-g]isoquinoline;

(±)-trans-2-Diethylaminocarbonyl-3,7-dimethyl-4a-(3-hydroxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[3,2-g]isoquinoline;

(±)-trans-2-Benzylaminocarbonyl-3,6-dimethyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline;

(±)-trans-2-Benzylaminocarbonyl-3,6-dimethyl-8a-(3-hydroxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride;

(±)-trans-3,6-Dimethyl-8a-(3-methoxyphenyl)-2-pyrrolidinocarbonyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline;

(±)-trans-3,6-Dimethyl-8a-(3-hydroxyphenyl)-2-pyrrolidinocarbonyl-

4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride;

(±)-trans-6-Ethyl-3-methyl-8a-(3-methoxyphenyl)-2-phenylaminocarbonyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline;

(±)-trans-6-Ethyl-8a-(3-hydroxyphenyl)-3-methyl-2-phenylaminocarbonyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline;

(±)-trans-2-Diethylaminothiocarbonyl-6-ethyl-3-methyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline;

(±)-trans-2-Diethylaminothiocarbonyl-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline;

(±)-trans-6-Cyclopropylmethyl-2-diethylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline hydrochloride;

(±)-trans-6-Cyclopropylmethyl-2-diethylaminocarbonyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline hydrochloride;

(±)-trans-2-Diisopropylaminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline;

(±)-trans-2-Diisopropylaminocarbonyl-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride;

(±)-trans-2-Aminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline;

(±)-trans-2-Aminocarbonyl-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline hydrochloride;

(±)-trans-6-Ethyl-2-ethoxycarbonyl-8a-(3-methoxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-3-trifluoromethyl-1H-pyrrolo[2,3-g]isoquinoline;

(±)-trans-6-Ethyl-2-ethoxycarbonyl-8a-(3-hydroxyphenyl)-4,4a,5,6,7,8,8a,9-octahydro-3-trifluoromethyl-1H-pyrrolo[2,3-g]isoquinoline hydrochloride;

(±)-trans-2-Diethylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-6-propyl-

4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride;

(±)-trans-2-Diethylaminocarbonyl-8a-(3-hydroxyphenyl)-3-methyl-6-propyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride;

(±)-trans-2-Dimethylaminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline;

(±)-trans-2-Dimethylaminocarbonyl-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride;

(-)-trans-2-Diethylaminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride;

(-)-trans-2-Diethylaminocarbonyl-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride;

(+)-trans-2-Diethylaminocarbonyl-6-ethyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride;

(+)-trans-2-Diethylaminocarbonyl-6-ethyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride;

(±)-trans-2-Diethylaminocarbonyl-6-(2-furylmethyl)-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline hydrochloride;

(±)-trans-2-Diethylaminocarbonyl-6-(2-furylmethyl)-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g] isoquinoline;

(±)-trans-2-Diethylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline;

(±)-trans-6-Butyl-2-diethylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline;

(±)-trans-6-Butyl-2-diethylaminocarbonyl-8a-(3-hydroxyphenyl)-3-methyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline;

(±)-trans-7-Ethyl-4a-(3-methoxyphenyl)-1-methyl-4,4a,5,6,7,8,8a,9-octahydro-2-

phenyl-1H-imidazo[4,5-g]isoquinoline;

(±)-trans-7-Ethyl-4a-(3-hydroxyphenyl)-1-methyl-4,4a,5,6,7,8,8a,9-octahydro-2-phenyl-1H-imidazo[4,5-g]isoquinoline;

(±)-trans-6-Ethyl-8a-(3-methoxyphenyl)-3-methyl-2-pyrrolidinocarbonyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride;

(±)-trans-6-Ethyl-8a-(3-hydroxyphenyl)-3-methyl-2-pyrrolidinocarbonyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrrolo[2,3-g]isoquinoline;

(±)-trans-2-Diisopropylaminocarbonyl-8a-(3-methoxyphenyl)-3-methyl-6-propyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride, and

(±)-trans-2-Diisopropylaminocarbonyl-8a-(3-hydroxyphenyl)-3-methyl-6-propyl-4,4a,5,6,7,8,8a-octahydro-1H-pyrrolo[2,3-g]isoquinoline hydrochloride.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 and a pharmaceutically acceptable carrier.

8. A compound according to any one of claims 1 to 6 for use as an active therapeutic substance.

9. A compound according to any one of claims 1 to 6 for use in the treatment of pain or as an immunomodulating and/or cardiovascular agent.

10. The use of a compound according to any one of claims 1 to 6 in the manufacture of a medicament for the treatment of pain or as an immunomodulating and/or cardiovascular agent.

11. A method for the treatment and/or prophylaxis of pain and of rejection of transplants and skin grafts in mammals particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of a compound according to any one of claims 1 to 6.

INTERNATIONAL SEARCH REPORT

Internat l Application No
PCT/EP 94/02325

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 A61K31/435 C07D498/04 C07D491/048 C07D513/04 C07D495/04 //(C07D471/04,221:00,209:00),(C07D471/04,235:00, 221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,93 01186 (ZAMBELETTI) 21 January 1993 cited in the application see page 1, line 26 - line 29; claims 1,11	1,10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 November 1994	21. 11. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/EP 94/02325

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 11 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna tional Application No
PCT/EP 94/02325

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9301186	21-01-93	AU-A- 2194892	11-02-93
		EP-A- 0596897	18-05-94